OnePoint®
PATIENT CARE

What one can do.®

3rd Edition

Clinical Symptom Guide

Joe Solien, PharmD, BCPP, BCGP
Melissa Corak, PharmD
John Corrigan, PharmD

OnePoint®
PATIENT CARE

What one can do.®

3rd Edition

Clinical Symptom Guide

Joe Solien, PharmD, BCPP, BCGP
Melissa Corak, PharmD
John Corrigan, PharmD

OnePoint Patient Care
8130 Lehigh Ave.
Morton Grove, IL 60053-2627

www.onepointpatientcare.com

v3.0

OnePoint®
PATIENT CARE

What one can do.®

CONTRIBUTOR BIOS

Joe Solien, PharmD, BCPP, BCGP
Vice President of Clinical Services
Primary Author

Joe is responsible for OnePoint Patient Care's national clinical services programs, including staff and partner education, formulary design and development, and medication utilization reviews. He began working for OnePoint as a pharmacy student intern in 2004 and became a staff pharmacist after graduation. In 2010, he was promoted to Clinical Pharmacist and has continued to serve on the clinical team in a number of roles since then. Joe earned a PharmD from Midwestern University – Glendale and is board certified in both psychiatric and geriatric pharmacy. He earned a BS in biochemistry and molecular biology and a BA in chemistry from the University of Minnesota – Duluth.

Melissa Corak, PharmD
Senior Clinical Pharmacist
Primary Author

Melissa is the Senior Clinical Pharmacist at OnePoint Patient Care, primarily supporting the needs of pharmacy staff and hospice partners in OnePoint's Western Division. She has worked closely with the clinical team since joining OnePoint as a staff pharmacist in 2012 and transitioned to working with the team full-time in 2018. After completing her undergraduate studies at Arizona State University, Melissa earned her PharmD from Midwestern University – Glendale.

John Corrigan, PharmD
Clinical Pharmacist
Co-Contributor

John is a clinical pharmacist that primarily supports OnePoint Patient Care's Eastern Division. He has been a hospice pharmacist since 2014. He attended the University of Iowa for both undergraduate studies and pharmacy school. He graduated from the University of Iowa College of Pharmacy in 2013. He was first introduced to hospice and OnePoint Patient Care as a 4th year pharmacy student, completing a 5-week elective clinical hospice pharmacy rotation. He started his employment with OnePoint Patient Care as a staff pharmacist. He transitioned to his current role, as a clinical pharmacist, in the spring of 2019. His primary responsibilities are staff and partner education, medication utilization reviews, and assisting with formulary development and maintenance.

Rachel Kinn, PharmD, BCPPS
Primary Contributor - Pediatrics

Rachel completed her pharmacy school training at the University of Iowa College of Pharmacy. She went on to complete a PGY1 General Practice Residency at the University of Iowa Hospitals and Clinics and a PGY2 Pediatric Specialty Residency at The University of Iowa Stead Family Children's Hospital. She is currently practicing as a Clinical Pharmacy Specialist focusing in Pediatric Endocrinology and Neurology working with additional specialty teams including pain and palliative care and genetics. Rachel is a board certified pediatric pharmacotherapy specialist.

Rachel previously worked at OnePoint Patient Care as a pharmacy intern and PBM technician.

Kellie Goodlet, PharmD, BCPS, BCIDP
Primary Contributor - Infectious Disease

Kellie is an Assistant Professor at Midwestern University College of Pharmacy and a Faculty Clinical Pharmacist at St. Joseph's Hospital and Medical Center in Phoenix, Arizona. She completed her Doctor of Pharmacy at the University of Arizona and a PGY1+PGY2 Infectious Diseases Pharmacy Residency at Hartford Hospital. Dr. Goodlet is an active member of the Society of Infectious Diseases Pharmacists, Infectious Diseases Society of America, and the American Society of Health-System Pharmacists. Her research interests include antimicrobial stewardship and the management of drug resistance and opportunistic infection in immunosuppressed patient populations.

PRIOR CONTRIBUTORS

Gregory Dyke, BS RPh

Rishma Patel, PharmD, BCPS

Ian Castruita
Unfed Artist, LLC

Contents

OnePoint® PATIENT CARE

What one can do.®

OnePoint® PATIENT CARE

What one can do.®

Drug Monographs 462

Appendix APNDX•479

OnePoint® PATIENT CARE

What one can do.®

Preface

Implementation of Medicare Hospice Benefit in 1983 forever changed the practice of end-of-life care in the United States. The Benefit helped us recognize opportunities to change the focus of medical care for patients with life limiting illness from curative or restorative treatment to symptom management and whole-person care. As a result more patients with more types of disease are treated by hospice practitioners. This opened up new worlds of clinical practice and over the intervening years, medical, nursing and pharmaceutical care have evolved and grown to meet the ever changing needs of patients with life-limiting illness. With this increasing patient population and new professional opportunities come new practitioners to the field.

Clinical science does not stand still. Need, whether driven by disease, unmanaged symptom burden, or search for knowledge, does not stand still. These needs require us to have a common understanding of the causes of disease, associated symptom burden and management of these symptoms. They require us, collectively, to share our knowledge and expertise.

Symptom management continues to rely heavily upon knowledgeable prescribing. As such, navigating the art and science of appropriate medication use is essential. Additionally, understanding other tenets such as therapeutic substitution and deprescribing are necessary to effect person-centered pharmaceutical care.

Finally, in today's regulatory environment, it is equally important to understand the rules and regulations that apply to medication use and payment for medications for the hospice patient.

This Guide is intended to be an easy-to-use reference providing basic, evidence-based information to enable practitioners to identify symptoms commonly experienced by EOL patients, their relatedness to specific diseases, clinical insight how to manage them, drug therapy options and to understand how to navigate numerous drug therapy issues not specific to direct patient (pharmaceutical) care.

Joe Solien, PharmD, BCPP, BCGP
Vice President of Clinical Services
OnePoint Patient Care
2021

DEDICATION

This Guide is dedicated to the hospice nurses that care for patients as they transition through life-limiting illness to the ends of their lives as well as the loved ones that support them in their endeavors. We are humbled by their works.

ACKNOWLEDGEMENTS

The authors wish to thank our colleagues at OnePoint for their assistance, support and recommendations in compiling this text.

SPECIAL RECOGNITION

The Executive Management Team of OnePoint Patient Care for their support and encouragement throughout the process.

OnePoint®
PATIENT CARE

What one can do.®

How to Use This Guide

OnePoint® PATIENT CARE

What one can do.®

For the best experience, view this guide using the latest version of Adobe® Acrobat Reader®[A], which can be downloaded at:

https://acrobat.adobe.com/us/en/acrobat/pdf-reader.html

This how-to section covers features that are specific for navigating the Clinical Symptom Guide, and does not cover the basic operations of Acrobat Reader®. For a beginner's guide and full user guide on using Acrobat Reader®, please visit this site:

https://helpx.adobe.com/support/reader.html

While this document may be viewed with other PDF readers, the full functionality of bookmarks, hyperlinks and cross-references may not be guaranteed. This how-to section references the features specifically for Acrobat Reader DC® on Microsoft Windows®[B] desktop environments. If you have questions about viewing this document on your mobile device or other platforms, please contact your OnePoint Patient Care representative for assistance.

GENERAL NAVIGATION – BOOKMARKS AND PAGE THUMBNAILS

Users can quickly jump to specific sections in this guide by using the bookmarks and page thumbnail features.

When viewing the document for the first time, look to the left side of the Adobe Reader screen and find the bookmark and page thumbnail icons:

Bookmark

Page Thumbnail

The bookmarks are designed to allow readers to quickly jump to any specific section – simply mouse click the section, monograph or appendix name to navigate to it.

Thumbnails allow for navigating based on page appearance, and are convenient for skipping ahead and back within a group of pages.

If you do not see the icons, go to View> Show/Hide> Navigation Panes> Bookmarks OR Page Thumbnails to reveal the section and the Navigation Pane.

A Adobe and Acrobat Reader are either registered trademarks or trademarks of Adobe Systems Incorporated in the United States and/or other countries.

B This Clinical Symptom Guide is an independent publication and is neither affiliated with, nor authorized, sponsored, or approved by, Microsoft Corporation.

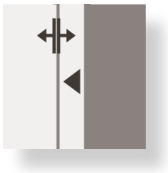
You may also look to see a vertical band on the left of the program window with a small arrow pointing toward the center of the screen:

Example of the Navigation Pane Arrow (Pane Closed)

Example of the Navigation Pane Arrow (Pane Open)

Click this arrow to collapse and expand the section containing the bookmarks and page thumbnails. The bookmark/page thumbnail column can also be expanded by hovering your mouse over the edge until you see the cursor change into a COLUMN RESIZE cursor. This is helpful for adjusting the layout to fit your specific screen.

Move cursor to the area next to the navigation pane arrow...



...the cursor changes to a COLUMN RESIZE cursor. Left click and hold when it appears to adjust the column size.

EMBEDDED NAVIGATION – TABLE OF CONTENTS AND HYPERLINKS

Within the Clinical Symptom Guide is text that allows readers to jump directly to the referenced subject.

The Table of Contents (TOC) functions exactly like the bookmarks section, but unlike the bookmark section the TOC doesn't remain viewable after a link is selected. Use it to quickly jump to a selected section by clicking on the page number or its corresponding description.

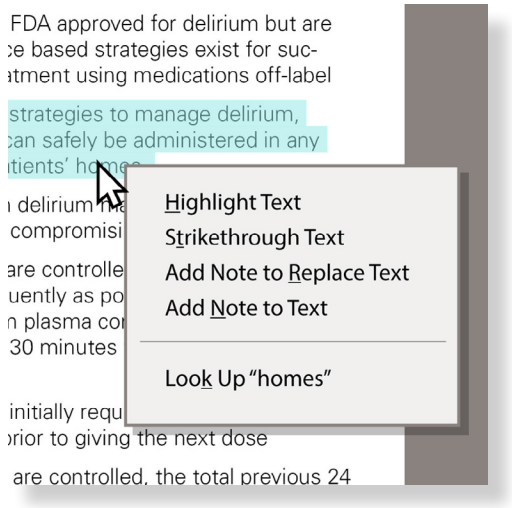
ANNOTATIONS AND ADDITIONS

There are several options for annotations in the guide, and all are considered "comments" which are logged under the comments column in Acrobat Reader®. When the comment feature is active, a toolbar showing assorted options for highlighting, underlining, notes, etc. is shown above the document. Whether the comment feature is active or not, you can always use the selection tool to use commenting features – but the comment column must be active to review and reply to previous comments. The selection tool is selected from the primary toolbar.

Selection Tool for Text and Images
(Not Active)

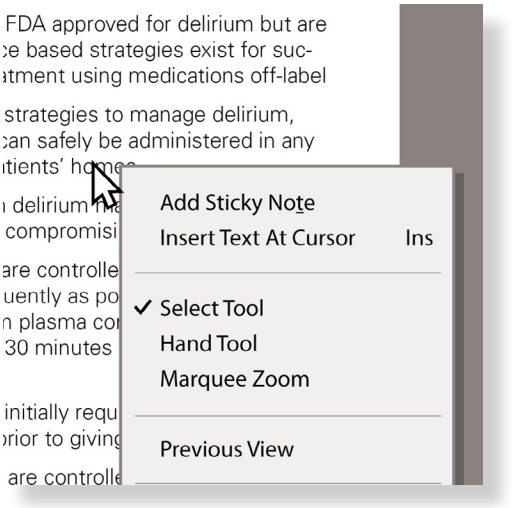
Selection Tool for Text and Images
(Active)

Most users will primarily use highlighting, commenting, and sticky notes while using the selection tool. To highlight, first select the text and then right click, then choose "highlight text". Selecting the text also allows users to "add a note". If no text is highlighted, a right click provides the option to leave a sticky note where ever the cursor is located.



Example of Right Click options after selecting text. The upper options are logged in the comments column.

The "look up" feature opens up a search window for the word indicated.



Example of Right Click options when no text is selected. The upper options are logged in the comments column.

Other readers may wish to add to their copy of the guide by using the "insert text" or "strikethrough text" features of the PDF. These options may prove useful for users that need to communicate specific information with peers and coworkers. Strikethrough leaves a red line through the selected text. Insert text provides a blue arrow at the cursor location. Each option is recorded in the comments.

To delete any comment, select it either in the document or within the comments column, then right click to show the delete option.

To edit typed comments, double click on the text within the instance inside the comments column. If you do not see the comment column, go to View> Tools> Comment to reveal the section. You may also look to see a vertical band on the right with a small arrow pointing toward the center of the screen.

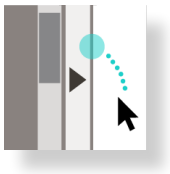
Example of the Tools Pane Arrow (Pane Closed)

Example of the Tools Pane Arrow (Pane Open)

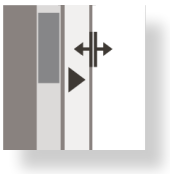
Click this arrow to collapse and expand the section containing the tools column. From there, you should see an option for "comment".

Comments Icon

Once selected, the comments column can also be expanded by hovering your mouse over the edge until you see the cursor change into a column resize cursor. This is helpful for adjusting the layout to fit your specific screen.



Move cursor to the area next to the tools pane arrow...



...the cursor changes to a COLUMN RESIZE cursor. Left click and hold when it appears to adjust the column size.

ACCESSIBILITY NOTE

This PDF document has been remediated to pass Adobe Acrobat's Accessibility Check, however individual user experience may vary based on the type of screen reader being used. For more information about computer accessibility software, we recommend visiting the following site:

https://www.afb.org/blindness-and-low-vision/using-technology/using-computer/part-ii-experienced-computer-user-new-0#reading

QUESTIONS/COMMENTS/ISSUE

If you have a question or concern related to the Clinical Symptom Guide's navigation (IE: broken links, bookmarks, etc.) or accessibility features, please email info@oppc.com with the subject line: CSG Feedback.

All fixes will be incorporated into future editions of the Clinical Symptom Guide; Thank you in advance for your time to help make this guide a useful tool for all.

Abbreviations

ABBREVIATION	DEFINITION
5-HT3	serotonin
ABG	arterial blood gas
AC	before meals
ACE	angiotensin converting enzyme
ADE	adverse drug event
AGS	American Geriatric Society
AIDS	Acquired Immune Deficiency Syndrome
ALS	Amyotrophic Lateral Sclerosis
APAP	acetaminophen
ARB	angiotensin receptor blocker
BID	two times day
BMI	Body Mass Index
BMP	basic metabolic panel
BP	blood pressure
BPH	benign prostatic hypertrophy
BUD	beyond use date
BUN	blood urea nitrogen
CBC	complete blood count
cGY	centi-Gray units
CHF	Congestive Heart Failure
CIC	Chronic Idiopathic Constipation
CKD	Chronic Kidney Disease
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CR	controlled release
CrCl	creatinine clearance
CTZ	chemoreceptor trigger zone
D2	dopamine type 2 receptor
DM	diabetes mellitus

ABBREVIATION	DEFINITION
DR	delayed release
EC	enteric coated
EES	erythromycin ethylsuccinate
EF	ejection fraction
EPS	extrapyramidal symptoms
ER	extended release
ESLD	end-stage liver disease
ESRD	end-stage renal disease
eg	for example
FDA	Food and Drug Administration
g	gram
GERD	Gastroesophageal Reflux Disease
GI	gastrointestinal
gtts	drops
H1	histamine-1 receptor
H2	histamine-2 receptor
H2RA	histamine-2 receptor antagonist
HCl	hydrochloride
HIV	Human Immunodeficiency Virus Infection
HPA	hypothalamic-pituitary-adrenal axis
HR	heart rate
HS	hour of sleep
IBS	Irritable Bowel Syndrome
ie	in other words; that is to say
IM	intramuscular
Inj	injection
IR	immediate release
IV	intravenous
K+	potassium
kg	kilogram

OnePoint® PATIENT CARE

What one can do.®

ABBREVIATION	DEFINITION
L	liter
LA	long acting
LMWH	low molecular weight heparin
LOC	level of consciousness
M1	muscarinic-1 receptor
MAOI	Monoamine Oxidase Inhibitor
mbq	megabecquerels
mcg	microgram
mCi	millicurie
MDD	maximum daily dose
mg	milligram
min	minute
ml	milliliter
N/V	nausea/vomiting
neb	nebulizer, nebulized solution
NK1	neurokinin-1 receptor
NNT	number needed to treat
NPO	nothing by mouth
NSAID	non-steroidal anti-inflammatory drug
NTE	not to exceed
O2	oxygen
ODT	orally disintegrating tablet
OIC	opioid induced constipation
OTC	over the counter
PC	after meals
PE	phenytoin equivalent
PFS	preservative free solution
PO	oral
PPI	proton pump inhibitor
PR	per rectum
PRN	as needed
Q	every
QAM	every morning
QD	daily

ABBREVIATION	DEFINITION
QHS	bedtime
QID	four times a day
QOD	every other day
QW	weekly (once a week)
SCr	serum creatinine
SE	status epilepticus
SL	sublingual
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SQ	subcutaneously
SSKI	saturated solution of potassium iodide
SSRI	Selective Serotonin Reuptake Inhibitor
STAT	immediately
SVN	small volume nebulized (solution)
TCA	tricyclic antidepressants
TIA	transient ischemic attack
TID	three times a day
USP	United States Pharmacopeia
UTI	urinary tract infection
WHO	World Health Organization
XL	extended release
XR	extended release

OnePoint® PATIENT CARE

What one can do.®

OnePoint®
PATIENT CARE

What one can do.®

Adult Symptom Monographs

Agitation

DEFINITION

An unpleasant state of extreme arousal or extreme emotional disturbance; perturbation. An agitated person may feel stirred up, excited, tense, uncooperative, or irritable.

CAUSES

- May be due to depletion of the neurotransmitter acetylcholine, coupled with an increase in the amount of dopamine in key areas of the brain that control mood and behavior.
- Unmet physical needs; eg,: soiled diaper, hunger
- Uncontrolled physical symptoms; eg,: untreated pain, insomnia
- Unmet psychological needs; eg,: social isolation
- Uncontrolled psychological symptoms or stressors
- Environmental changes; eg,: unfamiliar surroundings, overstimulation
- Medical illness; eg,: seizure disorder, fecal impaction, urinary retention, infection (esp. elderly), electrolyte disturbances (eg,: hypercalcemia), respiratory distress, brain metastases, dementia
- Medications; eg,: benzodiazepines (paradoxical behavioral through disinhibition), anticholinergics, levetiracetam, theophylline, amphetamines, steroids
- Intoxication or withdrawal from drugs of abuse (such as cocaine, marijuana, hallucinogens, PCP, or opiates)
- Alcohol intoxication/withdrawal
- Nicotine withdrawal

HOW TO RECOGNIZE SYMPTOM

- Agitation can be verbal or physical; aggressive or non-aggressive
- Examples of verbal aggression include: screaming, inappropriate language
- Examples of physical aggression include: hitting, scratching, biting
- Examples of verbal non-aggression include: repeated requests for attention, excessive complaining, or interrupting despite adequate care
- Examples of physical non-aggression include: pacing, restlessness and wandering

CLINICAL INSIGHTS

- The first step in treatment is to attempt to identify and correct underlying causes of agitation.
- Non-pharmacological measures such as touch, verbal reassurances and a familiar, subdued environment may be helpful in mild to moderate agitation.
- Consider pharmacotherapy if attempts to correct underlying cause(s) and non-pharmacological measures fail and symptoms represent a danger to self or others.
- Haloperidol is considered first line therapy unless contraindicated (Avoid in patients with Parkinson disease, dementia with Lewy bodies, or if prior adverse reaction such as extrapyramidal symptoms or tardive dyskinesia.)
- For acute agitation, consider IM administration of medication to manage condition
- If benzodiazepines are used, monitor for paradoxical reactions, especially in patients with dementia, a history of prior head trauma or frontal lobe degeneration or ALS
  - » Common paradoxical reactions include behavioral disinhibition, excitement, or increased talkativeness after medication administration
- Valproic acid derivatives should be avoided in agitated patients with dementia because pooled evidence suggests they are harmful and ineffective.
- Regardless of the medication being used, use the lowest possible doses for the shortest possible duration to minimize adverse reactions
- Symptom differentiation
  - » Agitation and apathy often occur in the same individual; sedatives used to treat agitation can worsen apathy and stimulants used to treat apathy often worsen agitation
  - » Agitation and delirium are discrete symptoms; agitation may be a symptom of delirium, which is an acute mental status change often accompanied by psychosis

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BENZODIAZEPINES				
Alprazolam (Xanax)	Initial: 0.25mg TID scheduled or PRN MDD: 8mg/day	Oral Disintegrating Tablet (ODT): 0.25mg, 0.5mg, 1mg, 2mg Oral solution: 1mg/ml Tablet: 0.25mg, 0.5mg, 1mg, 2mg	• Short acting • Intermediate onset • May produce rebound anxiety between doses as tolerance develops • Highest risk for withdrawal if tolerant patient abruptly stops using medication • Oral solution is more expensive than tablets	Y
Diazepam (Valium)	Initial: 2mg BID scheduled or PRN MDD: 40mg/day	Oral solution: 5mg/ml Solution for injection: 5mg/ml Tablet: 2mg, 5mg, 10mg	• Long acting, active metabolites may accumulate and contribute to sedation • Most rapid onset of action with single dose • PO:INJ is 1:1 • Oral solution is more expensive than tablets	Y
Lorazepam (Ativan)	Initial: 0.5mg BID –TID (scheduled or PRN) MDD: not established	Oral solution: 2mg/ml Solution for injection: 2mg/ml, 4mg/ml Tablet: 0.5mg, 1mg. 2mg	• Short acting • Intermediate onset • No active metabolites; benzodiazepine of choice in hospice • PO:INJ is 1:1 • Oral solution is more expensive than tablets	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIDEPRESSANTS				
Citalopram (Celexa)	Initial: 10mg PO QD MDD: 40mg/day	Oral solution: 10mg/5ml Tablet: 10mg, 20mg, 40mg	• Most studied SSRI in demented patients • Max daily dose is 20mg per day in elderly patients and those with significant liver disease due to risk for QT-interval prolongation • Showed similar benefit to risperidone in clinical study of agitated dementia patients • Slow onset of 2-4 weeks; not beneficial for acute symptoms • Oral solution more expensive than tablets	Y
Trazodone (Desyrel)	Initial: 25-100mg PO bedtime MDD: 600mg/day	Tablet: 50mg, 100mg, 150g, 300mg	• May also improve comorbid depression if present • Sedating	Y
ANTIPSYCHOTICS				
Chlorpromazine (Thorazine)	Initial (PO): 10-50mg PO/PR/SLq4-6h Initial (INJ): 10-25mg IM/IV q4-6h PRN MDD (PO): 2,000mg/day MDD (INJ): 500mg/day	Solution for injection: 25mg/ml Tablet: 10mg, 25mg, 50mg, 100mg, 200mg	• Higher sedation index than haloperidol • Can cause orthostasis • Can be compounded as a suppository • IV must be administered slowly, NTE 1mg/min • Expensive	Y
Haloperidol Decanoate (Haldol Decanoate)	Initial: 50-100mg IM q month Initial dose is 10-20x the daily oral dose; maintenance dose is 10-15x the daily oral dose. For doses greater than 100mg, give 100mg, then give the balance of the dose 3-7 days later Maximum monthly dose: 450mg	Solution for injection: 50mg/ml, 100mg/ml	• Low sedation Index • Should not be used for initial therapy • Do not confuse with haloperidol lactate • Consider for non-compliant patients whose agitation endangers themselves or others *(Continued on next page)*	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIPSYCHOTICS (CONTINUED)				
Haloperidol (Haldol)	Initial: 0.5mg-1mg Q4-6 hours scheduled or PRN MDD: 100mg/day	Oral solution: 2mg/ml Solution for injection: 5mg/ml Tablet: 0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg	• Useful if patient is unable to tolerate benzodiazepines • May produce extrapyramidal symptoms, Tardive dyskinesia • Do not give haloperidol decanoate IV, should only be administered IM • May prolong QT interval • PO:INJ (lactate) is 2:1 • Injection is expensive	Y
Olanzapine (Zyprexa)	Initial: 2.5-5mg PO QD MDD: 20mg/day	Oral Disintegrating Tablet (ODT)* (Zydis formulation): 5mg, 10mg, 15mg, 20mg Solution for injection: (administer IM only) 10mg Tablet: 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg	• Doses greater than 10mg per day not typically more effective • Cigarette smoking reduces blood concentrations • More likely to cause weight gain than other atypical antipsychotics • Consider ODT formulation for non-cooperative patients or those with dysphagia • May affect glycemic control • May cause orthostasis • Expensive	Y/N*
Quetiapine (Seroquel)	Initial: 12.5-25mg PO BID-TID MDD: 800mg/day	Tablet: 25mg, 50mg, 100mg, 200mg, 300mg, 400mg Tablet (ER)* (brand only): 50mg, 150mg, 200mg, 300mg, 400mg	• Lowest incidence of extrapyramidal symptoms among antipsychotics. • Preferred if antipsychotic use is warranted in patients with Parkinson disease or dementia with Lewy bodies • Highly sedating • Do not crush ER tablets • May affect glycemic control • May cause orthostasis • Expensive *(Continued on next page)*	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIPSYCHOTICS (CONTINUED)				
Risperidone (Risperdal)	Initial: 0.25-0.5mg PO BID MDD: 16mg/day	Orally Disintegrating Tablet (ODT): 0.5mg, 1mg, 2mg Oral solution: 1mg/ml Tablet: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg	• Do not split or chew orally disintegrating tablet, will dissolve under the tongue within seconds • Highest risk of extrapyramidal symptoms among atypical antipsychotics; esp. if daily dose >6mg • May affect glycemic control • May cause orthostasis • Orally disintegrating tablets are more expensive than conventional tablets • Expensive	Y
ANTICONVULSANTS				
Carbamazepine (Tegretol)	Initial: 200mg PO BID MDD: 1,600mg/day	Chewable tablet: 100mg Oral suspension: 100mg/5ml Tablet: 200mg Tablet (ER)*: 100mg, 200mg, 300mg, 400mg	• May be preferred if comorbid seizure disorder • Commonly causes drug-drug interaction as a potent enzyme inducer • Not first line therapy	Y/N*
Divalproex (Depakote)	Initial (DR): 125-250mg PO BID Initial (ER) 250mg PO QD MDD (All): 60mg/kg/day	Sprinkle capsule (DR): 125mg Tablet (DR)*: 125mg, 250mg, 500mg Tablet (ER)*: 250mg, 500mg	• ER tablets are approximately 8-20% less bioavailable than DR tablets • Commonly causes tremor • May be preferred if comorbid seizure disorder • More expensive than valproic acid	Y/N*
Gabapentin (Neurontin)	Initial: 100mg PO TID Titrate q72h MDD: 3,600mg/day	Capsule: 100mg, 300mg, 400mg Oral solution: 250mg/5ml Tablet: 100mg, 300mg, 400mg, 600mg, 800mg	• Commonly causes dizziness; use caution in ambulatory patients • May also benefit comorbid neuropathic pain • Must be renally dose adjusted • May be preferred if comorbid seizure disorder	Y
Phenobarbital (Luminal)	Initial: 60-120mg PO/ PR/IM/ IV q4h PRN Titrate up 200mg q4h MDD: 3,800mg/day	Oral solution: 20mg/5ml Solution for injection: 60mg/ml, 65mg/ml, 130mg/ml Tablet: 15mg, 30mg, 32.4mg, 60mg, 64.8mg, 100mg	• Can be administered rectally or parenterally for severe symptoms • May be preferred if comorbid seizure disorder • Convenient daily dosing for seizure prevention *(Continued on next page)*	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICONVULSANTS (CONTINUED)				
Valproic Acid (Depakene)	Initial: 125-250mg PO BID MDD: 60mg/kg/day	Capsule: 250mg Oral solution: 250mg/5ml	• Approximately ½ cost of divalproex • May cause more G.I. related adverse effects than divalproex • Do not crush capsules • 1:1 conversion with divalproex DR • Commonly causes tremor • May be preferred if comorbid seizure disorder	N
OTHER				
Dextromethorphanquinidine (Nuedexta)	Initial: 20/10mg PO QD x 7 days, then increase to BID MDD: 40mg dextromethorphan-20mg quinidine/day	Capsule: 20mg dextromethorphan-10mg quinidine	• Off-label use • Generally well-tolerated • Can be compounded as an oral suspension • Expensive	Y

References

- American Geriatrics Society – A Guide to Dementia Diagnosis and Treatment, accessed online at: http://unmfm.pbworks.com/f/American+Geriatric+Society+Dementia+Diagnosis+03-09-11.pdf
- Ballard, C. et al. Dextromethorphan and quinidine for treating agitation in patients with Alzheimer disease dementia, JAMA, 2015; 314(12):1233.
- Baillon SF, et al. Valproate preparations for agitation in dementia. Cochrane Database of Systematic Reviews 2018, Issue 10. Art. No.: CD003945.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 688.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 182-189.
- Corbett, A. et al. Dextromethorphan and quinidine are suitable for off-label short-term treatment of agitation in people with Alzheimer's disease following first-line non-drug approaches, BMJ, 2016; 21(1):25.
- Cummings, J. et al. Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia, JAMA, 2015; 314(12):1242.
- Cummings, J. et al. Guidelines for Managing Alzheimer's disease: Part II. Treatment, American Family Physician, 2002;65:2263-72.
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 54.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 1382.
- Lexicomp charts and special topics: Antipsychotic Agents; accessed Nov. 2015.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Moore, A. et al. Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, Canadian Family Physician, 2014, Vol. 60 pp. 433-8.
- Pollock, B. et al. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients, Am J Psychiatry, 2002 159:460-465.
- Porsteinsson, A. et al. Effect of Citalopram on Agitation in Alzheimer Disease, The CitAD Randomized Clinical Trial, JAMA, 2014;311(7):682-691.
- Press, D. et al. Management of neuropsychiatric symptoms of dementia, UpToDate, literature current through Nov. 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 335.
- Schneider, L. et al. Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease, New England Journal of Medicine, 2006;355:1525-38.
- Schwab, W. Psychiatric symptoms of dementia: treatable, but no silver bullet, Cleveland Clinic Journal of Medicine, 2009, Vol.76 No.3, pp. 167-74.
- Shah, S. et al. Treatment of Alzheimer's disease across the spectrum of severity, Clinical Interventions in Aging, 2006:1(2) 131-42.
- Stefanacci, R. et al. Improving the Management of Disruptive Behavior and Reducing Antipsychotic Medications in Nursing Facility Residents, The Consultant Pharmacist, 2014, Vol. 29 No.12, pp.797-809.
- Sultzer, D. et al. A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia, American Journal of Psychiatry, 1997 Vol. 5 No. 1, pp. 60-69.
- Teri, L. et al. Treatment of agitation in AD, A randomized, placebo-controlled clinical trial, Neurology, 2000, No. 55, pp. 1271-8.
- Wahler, R. et al. Use of compounded dextromethorphan-quinidine suspension for pseudobulbar affect in hospice patients, J of Pall Med, 2017; 20(3):294.
- Winslow, B. et al. Treatment of Alzheimer Disease, American Family Physician, Vol.83 No.12, 2011.
- Woodward, M. Pharmacological treatment of challenging neuropsychiatric symptoms of dementia, Journal of Pharmacy Practice and Research, 2005, Vol.35 No.3, pp. 228-34.

Angina

DEFINITION

Chest pain that is the result of the heart muscles not receiving enough oxygen-rich blood.

CAUSES

- Exertion, anxiety or stress in patients with predisposing cardiac conditions
- Coronary artery atherosclerosis is the most common cause
- Other cardiac conditions that may cause angina include MI, hypertrophic cardiomyopathy, arrhythmias, aortic stenosis/insufficiency/dissection, valvular disease, uncontrolled hypertension
- Pulmonary hypertension
- Blood clots

HOW TO RECOGNIZE SYMPTOM

- Discomfort or pain may be described as pressure, squeezing, constriction, choking, burning, tightness, or a knot in chest, jaw, shoulder, back or arms
- Pain and discomfort are more often diffuse and visceral, rather than localized
- Typically gradual in onset and offset, lasting up to 30 minutes
- Elicited by activities that increase myocardial oxygen demand
- Often accompanied by other symptoms such as dyspnea, nausea or sweating
- Pattern of pain often may be reproducible after a specific amount of exertion

CLINICAL INSIGHTS

- Episodic chest pain may be due to a variety of non-cardiac sources, such as GERD or dyspepsia, which should be treated separately
- Elderly, female or diabetic patients may not present with typical angina symptoms
- Symptoms may be alleviated by rest and/or nitroglycerin to reduce myocardial oxygen demand
- Nitroglycerin causes a marked lowering of blood pressure; monitor carefully when used with other antihypertensives
- For frequent angina, in addition to symptomatic treatment with nitroglycerin, consider adding a long-acting nitrate to prevent symptoms.
- Nitrate-free periods of 8-12 hours per day are crucial to avoid tolerance to nitrate-containing products and ensure effective treatment
- Beta-blockers are drugs of choice for angina due to stable ischemic heart disease
- Nitroglycerin should be considered as initial therapy for episodic symptoms
- Consider calcium channel blockers if beta-blockers are contraindicated
- Combination of nitrates plus beta-blocker or calcium channel blocker may provide synergistic symptom improvement

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OPIOIDS				
Morphine Sulfate	Initial: 5-10mg PO/SL Q1-4 hours PRN	Oral solution: 10mg/5mL, 20mg/5mL, 20mg/ml Tablet: 15mg, 30mg	• May be used in treatment of unstable angina when symptoms not relieved with nitroglycerin or despite adequate anti-ischemic therapy	Y
NITRATES				
Nitroglycerin (Nitrostat, Nitromist, Nitro-Bid, Nitro-Dur, Nitro-Time)	Initial (SL tablet): 0.3-0.6mg q5min for max of 3 doses in 15 min MDD (SL tablet): not established Initial (SL spray): 1-2 sprays SL Q3-5min for max of 3 doses in 15 min Initial (transdermal ointment): 0.5inch ribbon topically upon arising, repeated 6 hours later MDD (transdermal ointment): two 2-inch applications Initial (transdermal patch): 0.2-0.4mg/hr for 12-14h/day MDD (transdermal patch): 0.8mg/hr patch for 12-14h/day Initial (ER capsule): 2.5mg PO TID-QID MDD (ER capsule): 104mg/day	Capsule (ER): 2.5mg, 6.5mg, 9mg Sublingual spray: 400mcg/spray Tablet (SL): 0.3mg, 0.4mg, 0.5mg Transdermal ointment: 2% Transdermal patch: 0.1mg/hr, 0.2mg/hr, 0.4mg/hr, 0.6mg/hr	• Do not crush or chew sublingual tablets • Be sitting or in resting position to prevent falls from expected side effects of acute hypotension • Contraindicated with concomitant use of PDE-5 inhibitors such as Viagra • Must store tablets in their original container away from heat, moisture, light • Rotate patch sites and allow nitrate-free intervals • Commonly causes headache • May instruct patient to call hospice if no relief after three SL doses • Spray significantly more expensive than sublingual tablets	N
Isosorbide Dinitrate (Isordil, Dilatrate)	Initial (IR tablet): 5-20mg PO BID-TID MDD (IR tablet): 240mg/day Initial (ER tablet): 40mg PO QD-BID MDD: 160mg/day	Tablet: 5mg, 10mg, 20mg, 30mg Tablet (ER)*: 40mg	• When prescribed BID, consider 8AM and afternoon administration to allow nitrate-free interval overnight • Allow nitrate free intervals of ≥ 14hours for immediate release, > 18 hours for ER • Do not crush ER tablet *(Continued on next page)*	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NITRATES (CONTINUED)				
Isosorbide Mononitrate (Ismo, Imdur)	Initial (IR tablet): 5-20mg PO BID with doses given 7h apart MDD (IR tablet): 40mg/day Initial (ER tablet): PO: 30-60mg PO QAM MDD (ER tablet): 240mg/day	Tablet: 10mg, 20mg Tablet (ER)*: 30mg, 60mg, 120mg	• IR tablet should be scheduled with doses 7 hours apart, starting in the morning • Do not crush or chew ER tablet • Allow nitrate free intervals of ≥ 14hours for immediate release	Y/N*
BETA-BLOCKERS				
Metoprolol (Lopressor, Toprol XL)	Initial (IR tablet): 50mg PO BID MDD (IR tablet): 400mg/day Initial (ER tablet): 100mg PO QD MDD (ER tablet): 400mg/day	Tablet: 25mg, 50mg, 100mg Tablet (ER)*: 25mg, 50mg, 100mg, 200mg	• Monitor for bradycardia • ER tablets may be split in half, but should not be crushed	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CALCIUM CHANNEL BLOCKERS				
Verapamil (Calan, Isoptin, Verelan)	Initial (IR tablet): 40-80mg PO TID Initial (24-hour ER): 180mg PO QHS MDD (all forms): 480mg/day	Tablet: 40mg, 80mg, 120mg Tablet (ER,12-hour)*: 120mg, 180mg, 240mg Tablet (ER, 24-hour)*: 100mg, 120mg, 180mg, 200mg, 240mg, 300mg, 360mg	• IR: start with 40mg per dose if elderly or small in stature • Causes less edema than other calcium channel blockers • May cause constipation, particularly in elderly patients • Do not crush extended release products • Consider dose reduction or lower starting doses in patients with liver disease	Y/N*
Diltiazem (Cardizem, Cartia, Taztia XT, Dilacor XR, Tiazac)	Initial (IR tablet): 30mg PO QID MDD (IR tablet): 360mg/day Initial (12-hour ER): 60mg PO BID Initial (24-hour ER): 120mg PO QD MDD (ER forms): 540mg/day	Capsule (ER, 12-hour)*: 60mg, 90mg, 120mg Capsule (ER, 24-hour)*: 120mg, 180mg, 240mg, 300mg, 360mg, 420mg Tablet: 30mg, 60mg, 90mg, 120mg	• Long-acting formulations preferred • Use with caution in patients with conduction abnormalities, or severe systolic dysfunction • Monitor for bradycardia • Do not crush or open extended-release formulations • May cause peripheral or pulmonary edema as adverse effects	Y/N*
Amlodipine (Norvasc)	Initial: 2.5-5mg PO QD MDD: 10mg/day	Tablet: 2.5mg, 5mg, 10mg	• Start with 2.5mg if hepatic impairment • Preferred dihydropyridine calcium channel blocker in patients with low EF (<40%) • May cause peripheral or pulmonary edema as adverse effects	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIANGINALS				
Ranolazine (Ranexa)	Initial: 500mg PO BID MDD: 2,000mg/day	Tablet (ER): 500mg, 1,000mg	• Use contraindicated in patients with any level of hepatic impairment • May cause QT-interval prolongation • Use as adjunct therapy only if symptoms persist despite optimal dose titration of other agents • Has many drug interactions. Discuss potential changes to drug regimen prior to initiation of therapy • Expensive	N

References

- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 1262-3.
- Lexi-comp 5-minute clinical consult, Coronary Artery Disease and Stable Angina, accessed Nov. 2015.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Kannam, J. et al. Stable ischemic heart disease: Overview of care, UpToDate, literature review current through Nov. 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 339.
- Simons, M. et al. New therapies for angina pectoris, UpToDate, literature review current through Nov. 2015.
- Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 136-148.

Anorexia & Cachexia

DEFINITION

Anorexia is a lack or loss of appetite for food.

Cachexia is a complex, multi-dimensional condition characterized by weakness and muscle wasting of the body due to severe, chronic illness.

CAUSES

- Anorexia
  - » Primary causes at end of life:
    - ° Anxiety
    - ° Cancer
    - ° CHF
    - ° CKD
    - ° Dehydration
    - ° Dementia
    - ° Depression
    - ° Metabolic Disorders
    - ° Medication adverse effects
    - ° Pain
    - ° Parkinson disease
  - » Other causes:
    - ° Oral candidiasis
    - ° Ill-fitting dentures
    - ° Gastritis
    - ° Dry mouth
    - ° Gastroparesis (delayed gastric emptying)
    - ° Constipation
    - ° Bowel obstruction
    - ° GERD
    - ° Nutritional deficiencies
    - ° Liver metastases
    - ° Psychosocial issues
    - ° Stroke
    - ° Altered perception of food
- Cachexia:
  - » Primary causes at end of life:
    - ° Cancer
    - ° CHF
    - ° CKD
    - ° Dementia
    - ° HIV/AIDS
    - ° Metabolic disorders
    - ° Medication adverse effects
    - ° Motor neuron disease / ALS
    - ° Parkinson disease
    - ° Cystic fibrosis
  - » Other causes:
    - ° Other severe, chronic illness
    - ° Sepsis
    - ° Chemotherapy / radiation
    - ° Catabolic states
    - ° Gastrointestinal issues
- Drugs that may contribute to anorexia / cachexia
  - » Psychostimulants
  - » SSRI type antidepressants
  - » Topiramate
  - » Opioids
  - » Caffeine
  - » Nicotine
  - » Illegal stimulant drugs such as cocaine or methamphetamine

HOW TO RECOGNIZE SYMPTOM

- Anorexia and/or cachexia:
  - » Weight loss
- Anorexia:
  - » Decreased appetite or intake
  - » Reduced physical functioning
- Cachexia
  - » Fatigue
  - » Physical wasting
    - ° Involuntary weight loss > 5% in the past 6 months OR weight loss > 2% in patients with a BMI <20kg/m^2 or skeletal muscle sarcopenia

CLINICAL INSIGHTS

- Anorexia:
  - » Anorexia is highly prevalent and commonly experienced by terminally ill patients.
  - » Eliminate dietary restrictions. Encourage patients and families to think of food as a comfort measure and advise offering favorite foods regardless of nutritional value.
  - » Consider supplementation with high calorie / high protein supplements.
  - » Supportive measures include: good mouth care (including denture fit evaluation).
  - » Aggressive nutritional support is rarely beneficial; offer oral support, rather than IV feedings
  - » Medications such as megestrol, oxandrolone and thalidomide have limited effectiveness and adverse effects often outweigh benefits
  - » Metoclopramide may be used to increase gastric motility / reduce stomach emptying time.
  - » When present, management of underlying depression may benefit appetite
  - » Consider a dietician referral if necessary
- Cachexia:
  - » Cachexia is expected to be experienced by a significant number of hospice patients. Cachexia does not equal starvation
  - » Family education regarding the aspects of cachexia is essential in order to set realistic goals and minimize patient distress and frustration
  - » Utilize a physical assessment tool to rule out reversible factors, such as pain, oral cavity sores/ infection, constipation and nausea/vomiting
  - » Involve the patient in the planning for their nutrition
  - » Emphasize the need for a balanced diet and exercise as tolerated
  - » High calorie / high protein supplementation may help to stabilize weight
  - » Utilize non-pharmacologic therapy, such as offering small portions of food, avoiding foods with a strong odor, and offering easy-to-swallow foods
  - » Megestrol can stimulate appetite in some patients but resulting weight gain, if any, is not muscle mass. No clear improvement in quality of life or prolongation of survival was seen in patients taking progestogens
  - » Weight gained due to drug therapy may not translate to improved strength or vigor
  - » Consult with a dietician as necessary

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CORTICOSTEROIDS				
Dexamethasone (Decadron)	Initial: 2-4mg PO QD MDD: not established for this indication	Oral solution: 0.5mg/5ml, 1mg/ml Tablet: 0.25mg, 0.5mg, 0.74mg, 1mg, 1.5mg, 2mg	• Most comprehensively studied corticosteroid in palliative care • Give dose in the morning to prevent insomnia • Beneficial where short term therapy is indicated • Start with low dose and monitor for efficacy weekly, can increase dose weekly upon reassessment • Preferred in patients w/ history of thromboembolism or at high risk for clots • Also useful for bone pain or bronchospasm	Y
Prednisone	Initial: 10mg PO QD MDD: not established for this indication	Oral solution: 1mg/ml, 5mg/ml Tablet: 1mg, 2.5mg, 5mg, 10mg, 20mg, 50mg Tablet (DR)*: 1mg, 2mg, 5mg	• Effective dose varies • Give dose in the morning to prevent insomnia • Start with low dose and monitor for efficacy weekly • Titrate up by 2-5mg at weekly intervals if needed • Indicated when short term therapy may be beneficial (less than 6 weeks) • Also useful in treating bone pain, asthenia, or bronchospasm • Less expensive than dexamethasone	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIDEPRESSANTS				
Mirtazapine (Remeron)	Initial: 7.5mg PO QD MDD: 45mg/day	Oral disintegrating tablet (ODT)*: 15mg, 30mg, 45mg Tablet: 15mg, 30mg, 45mg	• Give dose at bedtime due to sedation • Most weight gain to be expected during first 4 weeks of use • Consider in patients with insomnia or depression combined with loss of appetite and weight loss • Lower doses are more sedating (7.5mg – 15mg) and more likely to stimulate appetite while higher doses are more often required for depression	Y/N*
PROGESTINS				
Megestrol (Megace)	Initial: 160mg PO QD MDD: 800mg/day	Oral suspension: 40mg/ml, 625mg/5ml (brand only) Tablet: 20mg, 40mg	• Initial dose variable based on underlying disease state • Daily doses over 800mg have not been shown to alter therapeutic response • Not recommended if life expectancy is less than 30 days • Weight gained is primarily fat rather than lean body mass • Reassess at 2-4 weeks for efficacy • Document weight every 2 weeks, if no response, taper and discontinue therapy after 4-8 weeks • Benefit for more than 12 weeks has not been established • Contraindicated in patients with history of thromboembolic disease • Adverse effects include: peripheral edema, hyperglycemia, hypertension and adrenal gland effects. • Suspension is preferred over tablets due to tablet burden necessary for optimal dose • Avoid in patients with limited mobility • A large retrospective study of more than 17,000 nursing home patients found reduced survival and no effect on appetite	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CANNABINOIDS				
Dronabinol (Marinol)	Initial: 2.5mg PO BID MDD: 20mg/day	Capsule: 2.5mg, 5mg, 10mg	• Schedule III controlled substance; abuse potential exists (contains one of the active ingredients in marijuana) • Elderly patients may be more susceptible to adverse effects • A number of randomized studies have not demonstrated efficacy for weight gain • May be useful if comorbid pain or nausea/vomiting • Expensive	N
ANABOLIC STEROIDS				
Oxandrolone (Oxandrin)	Initial: 2.5-5mg PO BID MDD: 20mg/day; 10mg/day if elderly	Tablet: 2.5mg, 10mg	• Typically used as adjunct therapy • Dose is titrated based on response • Typical duration of therapy is 2-4 weeks and may be repeated if needed • Schedule III controlled substance with some abuse potential • Expensive	Y
ANTIHISTAMINES				
Cyproheptadine (Periactin)	Initial: 2mg PO QID MDD: 8mg/day	Oral solution: 2mg/5ml Tablet: 4mg	• May cause/worsen constipation, dry eyes, urinary retention • Can be used off-label for diarrhea • Not first line therapy; minimal benefit	Y

References

- Bodenner, D. et al. A retrospective study of the association between megestrol acetate administration and mortality among nursing home residents with clinically significant weight loss, The American Journal of Geriatric Pharmacology, 2007, 5(2):137-46.
- Bruera, E. et al. Palliative care: Assessment and management of anorexia and cachexia, UpToDate, Literature review current through Nov. 2015.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 538-541.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 230-231.
- Champion, A. Anorexia of aging, Annals of Long-Term Care: Clinical Care and Aging, 2011, 19(10):18-24.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3b: Anorexia / Cachexia, accessed online Nov. 2015 at: http://www.cancer.gov/resources-for/hp/education/epeco/self-study/module-3/module-3b.pdf
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 60-63.
- Goodlin, S. End-of-Life Care in Heart Failure, Current Cardiology Reports, 2009, 11:184-91.
- Goodnick, PJ, et al., Weight Change during Mirtazapine Therapy, *Primary Psychiatry*, 1998: Vol. 3, pp. 103-108.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 888-915,1475-6.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 168-9.
- Temel, J. et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomized, double-blind, phase 3 trials, The Lancet, 2016; 17:519.

Anxiety

DEFINITION

A subjective state of worry, apprehension, uncertainty or emotional discomfort that may or may not be inappropriate in a given situation.

CAUSES

- Interpersonal, spiritual, or existential causes
- Medical conditions, such as:
  - Psychological disorders: post-traumatic stress disorder, generalized anxiety disorders, phobia, obsessive compulsive disorder
  - Other psychiatric symptoms that may contribute to anxiety:
    - Delirium, depression, psychosis, mania
  - Pulmonary disease
  - Cardiac disease
  - ALS or other neuromuscular disease
  - Hyperthyroidism
  - Infection
- Untreated pain
- Sleep deprivation
- Medications:
  - steroids
  - bronchodilators
  - psychostimulants
  - decongestants
  - theophylline
  - levetiracetam
- Other substances:
  - caffeine
  - nicotine
- Drug or substance withdrawal:
  - opioids
  - benzodiazepines
  - antidepressants
  - illegal drugs
- Illegal drugs:
  - cocaine
  - amphetamines

HOW TO RECOGNIZE SYMPTOM

- Behaviors include: excessive worrying, physical distress (tension, jitteriness, or restlessness), social withdrawal, avoidance, diminished coping, inability to relax or concentrate
- Observable signs of anxiety include: tense posture, fidgeting with fingers or clothing, frequent sighing, dryness or thickening of the lips, tremor or trembling, insomnia, changes in communication style
- Other signs may include: increased pulse/ respiratory rate, increased blood pressure, diaphoresis, flushing, dry mouth, and diarrhea

CLINICAL INSIGHTS

- Management includes drug as well as non-drug therapies
- If possible, reduce or discontinue medications that may be contributing to anxiety
- For some patients, prevention of anxiety by routine dosing of anxiolytics may be more effective than attempting to control it on a PRN basis
- Benzodiazepines may increase the risk of falls, sedation and memory impairment. Consider lower doses in elderly patients if benefits of use outweigh risks.
- Paradoxical reactions such as behavioral disinhibition or delirium may result from benzodiazepine use.
- Short-acting benzodiazepines are preferred in patients with renal impairment.
- When benzodiazepine use is ineffective or inappropriate, antipsychotics or antihistamines are potential alternate therapies
- SSRIs are often used for chronic anxiety disorders such as PTSD or OCD, although the anxiolytic effects of antidepressants may take weeks to appear.
- SSRIs or mirtazapine may also be considered for other types of anxiety, especially if comorbid depression is present.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BENZODIAZEPINES				
Alprazolam (Xanax)	Initial: 0.25mg TID scheduled or PRN MDD: 8mg/day	Oral disintegrating tablet (ODT): 0.25mg, 0.5mg, 1mg, 2mg Oral solution: 1mg/ml Tablet: 0.25mg, 0.5mg, 1mg, 2mg Tablet (XR): 0.5mg, 1mg, 2mg, 3mg	• Short acting • May produce rebound anxiety between doses as tolerance develops • Highest risk for withdrawal if tolerant patient abruptly stops using medication • Intermediate onset • Oral concentrate is more expensive than tablets	Y
Clonazepam (Klonopin)	Initial:0.5mg BID scheduled or PRN MDD: 6mg/day	Oral disintegrating tablet (ODT): 0.125mg, 0.25mg, 0.5mg, 1mg, 2mg Tablet: 0.5mg, 1mg, 2mg	• Long acting • Active metabolites may accumulate and contribute to sedation • Most potent benzodiazepine • Intermediate onset • Oral disintegrating tablet can be considered as a therapeutic alternative to lorazepam solution	Y
Diazepam (Valium)	Initial: 2mg BID scheduled or PRN MDD: 40mg/day	Oral solution: 5mg/ml Solution for injection: 5mg/ml Tablet: 2mg, 5mg, and 10mg	• Long acting, active metabolites may accumulate and contribute to sedation • Most rapid onset of action with single dose • Rapid onset • PO:INJ is 1:1 • Oral solution is more expensive than tablets	Y
Lorazepam (Ativan)	Initial: 0.5mg BID –TID scheduled or PRN MDD: 10mg/day	Oral solution: 2mg/ml Solution for injection: 2mg/ml, 4mg/ml Tablet: 0.5mg, 1mg, 2mg	• Short acting • No active metabolites • Usually considered benzodiazepine of choice in hospice • Intermediate onset • PO:INJ is 1:1 • Oral concentrate is more expensive than tablets	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIDEPRESSANTS				
Citalopram (Celexa)	Initial: 10mg PO QD MDD: 40mg/day	Oral solution: 10mg/5ml Tablet: 10mg, 20mg, 40mg	• Most studied SSRI in demented patients • Max daily dose is 20mg per day in elderly patients and those with significant liver disease • Oral solution more expensive than tablets	Y
Escitalopram (Lexapro)	Initial: 5-10mg PO QD MDD: 20mg/day	Oral solution: 5mg/ml Tablet: 5mg, 10mg, 20mg	• Faster onset of action than other SSRI • Max 10mg/day in elderly patients • Use with caution if CrCl < 30ml/min • S-enantiomer of citalopram; 10mg escitalopram = 20mg citalopram • Oral solution more expensive than tablets	Y
Fluoxetine (Prozac)	Initial: 10-20mg PO QD MDD: 80mg/day	Capsule: 10mg, 20mg, 40mg Oral solution: 20mg/5ml	• Longest half-life of all SSRIs; allows for natural taper if discontinued abruptly, thereby avoiding withdrawal symptoms	Y
Mirtazapine (Remeron)	Initial: 15mg PO QHS MDD: 45mg/day	Oral disintegrating tablet (ODT): 15mg, 30mg, 45mg Tablet: 15mg, 30mg, 45mg	• One study demonstrated similar efficacy to diazepam • Consider in patients with other symptoms that may benefit from use, including: depression, anorexia, itching, insomnia, pain	Y/N*
Paroxetine (Paxil)	Initial: IR: 10-20mg PO QD; ER: 12.5-25mg QD MDD (IR): 50mg/day; 40mg/day if elderly MDD (ER): 62.5mg/day; 50mg if elderly	Oral suspension (brand only): 10mg/5ml Tablet: 10mg, 20mg, 30mg, 40mg Tablet (ER): 12.5mg, 25mg, 37.5mg	• Most sedating and anticholinergic SSRI • Use with caution if CrCl < 30ml/min or if severe liver disease • Suspension more expensive than tablets	Y
Sertraline (Zoloft)	Initial: 25-50mg PO QD MDD: 200mg/day	Oral solution: 20mg/ml Tablet: 25mg, 50mg, 100mg	• More G.I. related adverse effects than other SSRIs • Most concentrated oral solution of all SSRIs making it potentially useful if dysphagia limits volume per dose	Y
Trazodone (Desyrel)	Initial: 25mg PO Q hour PRN MDD: not established for this indication	Tablet: 50mg, 100mg, 150mg, 300mg	• Sedating • Priapism is a rare, but serious ADE	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIPSYCHOTICS				
Chlorpromazine (Thorazine)	Initial (PO): 10mg-50mg Q 4h-8h scheduled or PRN MDD: 1,000mg/day	Solution for injection: 25mg/ml Tablet: 10mg, 25mg, 50mg, 100mg, 200mg	• Highly sedating; useful if more sedation is needed • Oral concentrate and suppositories can be compounded • Can cause orthostatic hypotension • PO:INJ is 4:1 • Expensive	Y
Haloperidol (Haldol)	Initial (PO, lactate injection): 0.5mg-1mg Q 4-6 hours scheduled or PRN MDD: 100mg/day	Oral solution: 2mg/ml Solution for injection (lactate): 5mg/ml Tablet: 0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg	• Useful if patient is unable to tolerate benzodiazepines • May produce extrapyramidal symptoms, tardive dyskinesia • Do not give haloperidol decanoate IV, should only be administered IM • PO:INJ (lactate) is 2:1 • Injection is more expensive than tablets	Y
Olanzapine (Zyprexa)	Initial: 2.5-5mg PO QD MDD: 20mg/day	Oral disintegrating tablet (ODT) (Zydis formulation)*: 5mg, 10mg, 15mg, 20mg Tablet: 2.5mg, 5mg, 10mg, 15mg, 20mg	• Doses greater than 10mg per day not typically more effective • Cigarette smoking reduces blood concentrations • More likely to cause weight gain than other atypical antipsychotics • Do not split or chew orally disintegrating tablet, will dissolve under the tongue within seconds • Expensive	Y/N*
Quetiapine (Seroquel)	Initial: 12.5-25mg PO BID-TID MDD: 800mg/day	Tablet: 25mg, 50mg, 100mg, 200mg, 300mg, 400mg Tablet (ER)* (brand only): 50mg, 150mg, 200mg, 300mg, 400mg	• Lowest incidence of extrapyramidal symptoms among antipsychotics. • Preferred if antipsychotic use is warranted in patients with Parkinson disease or dementia with Lewy bodies • Highly sedating • Do not crush ER tablets • Expensive	Y/N*
Risperidone (Risperdal)	Initial: 0.25-0.5mg PO BID MDD: 16mg/day	Oral disintegrating tablet (ODT): 0.5mg, 1mg, 2mg Oral solution: 1mg/ml Tablet: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg	• Do not split or chew orally disintegrating tablet, will dissolve under the tongue within seconds • Highest risk of extrapyramidal symptoms among atypical antipsychotics; esp. if daily dose >6mg • Orally disintegrating tablets are more expensive than conventional tablets • Expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MISCELLANEOUS				
Buspirone (Buspar)	Initial: 5-7.5mg PO BID MDD: 60mg/day	Tablet: 5mg, 7.5mg, 10mg, 15mg, 30mg	• Less sedation or cognitive/ psychomotor impairment than benzodiazepines. • Delayed onset of efficacy of ~2-3 weeks, therefore not useful for acute anxiety symptoms • More expensive than benzodiazepines	Y
Diphenhydramine (Benadryl)	Initial: 12.5mg-50mg PO Q 4-8 hours PRN MDD: 300mg/day	Capsule: 25mg, 50mg Oral solution: 12.5mg/5ml Solution for injection: 50mg/ml Tablet: 25mg, 50mg	• Useful if sedation is necessary • Avoid in elderly or demented patients due to anticholinergic adverse effects • Antihistamine with mild anxiolytic and sedative properties • Useful for certain types of itching	Y
Gabapentin (Neurontin)	Initial: 100mg PO Q hour PRN MDD: 3,600mg/day	Capsule: 100mg, 300mg, 400mg Oral solution: 250mg/5ml Tablet: 100mg, 300mg, 400mg, 600mg, 800mg	• Wide effective dose range • Titrate to TID dosing for maximum efficacy unless contraindicated • Commonly causes sedation and dizziness; use caution in ambulatory patients. Start at low doses and titrate as tolerated. • Avoid using for this indication in patients with significant renal impairment • Adequate trial can require 2 months or more • No clinically significant drug interactions	Y
Hydroxyzine (Atarax, Vistaril)	Initial: 10mg – 25mg PO Q 6 hours scheduled or PRN May increase up to 100mg per dose MDD: 600mg/day	Capsule (Vistaril)*: 25mg, 50mg Oral solution: 2mg/ml Solution for injection: 25g/ml, 50mg/ml Tablet (Atarax): 10mg, 25mg, 50mg	• Antihistamine with mildly anxiolytic, analgesic, and sedative properties • Useful for itching • Avoid in elderly or demented patients due to anticholinergic adverse effects	Y/N*
Propranolol (Inderal)	Initial (IR): 20-40mg PO BID MDD: 320mg/day	Tablet: 10mg, 20mg, 40mg, 60mg, 80mg Tablet (ER)*: 60mg, 80mg, 120mg, 160mg	• Potentially useful for chronic or situational anxiety • Avoid in patients with lung disease • Monitor for bradycardia	Y/N*

References

- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 683-4.
- Bystritsky, A. et al. Pharmacotherapy for generalized anxiety disorder, UpToDate, literature review current through Nov. 2015.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 333-337.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3c: Anxiety, accessed online Nov. 2015 at: http://www.ipcrc.net/epco/EPEC-O%20M03a-q%20Symptoms/EPEC-O%20M03c%20Anxiety/EPEC-O%20M03c%20Anxiety%20PH.pdf
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 54.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 634,707,796,809-10, 1067, 1339, 1454-1457.
- Irwin, S. et al. Overview of anxiety in palliative care, UpToDate, literature review current through Nov. 2015.
- Irwin, S. et al. Overview of anxiety in palliative care, UpToDate, content current through 5/10/17; accessed online 8/21/17.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Peet, M. et al. Propranolol and Atenolol in the Treatment of Anxiety, International Clinical Psychopharmacology, 1986, 1, 314-19.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 239.
- Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 829-850.

Ascites

DEFINITION

The abnormal accumulation of excess fluid within the peritoneal cavity from the congested portal system as a result of total body sodium and water excess.

CAUSES

- Liver cirrhosis is the most common cause
- Malignancy – most commonly ovarian cancer, but also with breast, colon, endometrial, pancreatic, prostate, and stomach cancers as well as with non-Hodgkin's lymphoma and multiple myeloma
- Congestive heart failure
- Tuberculosis
- Pulmonary hypertension
- Hepatitis B or C
- Dialysis

HOW TO RECOGNIZE SYMPTOM

- Abdominal distension
- May present along with other symptoms such as dyspnea, GERD, dyspepsia, feelings of fullness, constipation, or nausea and vomiting

CLINICAL INSIGHTS

- First-line treatment of ascites is a combination of furosemide and spironolactone at a 40mg:100mg ratio. The doses can be titrated every 3-5 days, maintaining the furosemide:spironolactone ratio to achieve a target weight loss of 0.5-1kg/day (weight loss of <0.5kg/day may be a more appropriate target in the absence of peripheral edema)
- Potassium sparing diuretics, such as spironolactone, may not be appropriate or the dose may need to be reduced if the patient has renal impairment due to the risk of hyperkalemia
- Malignant ascites is less likely to respond to diuretics
- Abstinence from alcohol and maintaining a low-sodium diet (<800mg sodium, 2grams sodium chloride) may reduce symptom burden through diuresis
- Consider using non-selective beta-blockers to treat ascites that arises from portal hypertension caused by liver cirrhosis
- Ascites increases the risk for infection (spontaneous bacterial infection). Patients that experience a rapid accumulation of ascitic fluid and are febrile may have infected ascitic fluid and may benefit from a course of antibiotics
- Ethacrynic acid (Edecrin) is the only loop diuretic that does not have a sulfa cross-reactivity. It is currently available as brand-only and is substantially more expensive than other loop diuretics
- Although abdominal girth measurements are frequently used as an indicator for fluid loss, they tend to be unreliable
- Approximate loop diuretic equivalency: **Furosemide 40mg = Bumetanide 1mg = Torsemide 10-20mg = Ethacrynic Acid 50mg**

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Bumetanide (Bumex)	Initial: 0.5-2mg PO/IV QD MDD: 10mg/day	Solution for injection: 0.25mg/ml Tablet: 0.5mg, 1mg, 2mg	• Useful if resistant to furosemide • Administer last dose prior to 4pm • Consider monitoring for hypokalemia • Loop diuretic	Y
Eplerenone (Inspra)	Initial: 25-50mg PO QD MDD: 100mg/day	Tablet: 25mg, 50mg	• Contraindicated in severe renal impairment • Potassium sparing diuretic • Potentially useful alternative if gynecomastia occurs with spironolactone use • More expensive than other potassium sparing diuretics	Y
Ethacrynic Acid (Edecrin)	Initial: 50mg PO QD MDD: 400mg/day	Tablet: 25mg	• Drug of choice for patients with sulfa allergy • Consider monitoring for hypokalemia • Loop diuretic	Y
Furosemide (Lasix)	Initial: 10-160mg PO/ PR QD-BID MDD: 600mg/day	Oral solution: 10mg/ml, 40mg/5ml Solution for injection: 40mg/4ml Tablet: 20mg, 40mg, 80mg	• First line • Give in combination with spironolactone as 40mg:100mg (furosemide:spironolactone) • Drug of choice for edema • Nebulized furosemide has been used to treat ascites • 2:1 oral to IV potency • Consider monitoring for hypokalemia • Loop diuretic	Y
Spironolactone (Aldactone)	Initial: 50mg PO daily Titrate up to 200mg daily MDD: 400mg/day	Tablet: 25mg, 50mg,100mg	• First line • Give in combination with furosemide as 40mg:100mg (furosemide:spironolactone) • Doses can be divided BID • Potassium sparing diuretic • Especially useful with ascites of CHF • Prevents third spacing • Contraindicated in severe renal impairment	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Torsemide (Demadex)	Initial: 10-20mg PO/IV daily MDD: 200mg/day	Solution for injection: 10mg/ml Tablet: 5mg, 10mg, 20mg, 100mg	• Useful if resistant to furosemide • Loop diuretic • Consider monitoring for hypokalemia	Y
Triamterene (Dyrenium)	Initial: 100mg PO BID MDD: 300mg/day	Tablet: 50mg, 100mg	• Contraindicated in severe renal impairment • Potassium sparing diuretic	Y
BETA-BLOCKERS				
Carvedilol (Coreg)	Initial: 3.125mg-6.25mg PO BID MDD: 50mg/day	Capsule (ER)*: 10mg, 20mg, 40mg, 80mg Tablet: 3.125mg, 6.25mg, 12.5mg, 25mg	• Consider if patient has liver cirrhosis to reduce portal hypertension • Titrate to resting HR of 55-60 beats/ min or as tolerated • Avoid if patient has comorbid lung disease • More likely to cause hypotension than other non-selective beta-blockers • Less studied than other non-selective beta-blockers for reduction of portal hypertension	Y/N*
Nadolol (Corgard)	Initial: 20-40mg PO QD MDD: 320mg/day	Tablet: 20mg, 40mg, 80mg, 120mg, 160mg	• Consider if patient has liver cirrhosis to reduce portal hypertension • Titrate to resting HR of 55-60 beats/ min or as tolerated • Reduce dose in renal insufficiency • Avoid if patient has comorbid lung disease	Y
Propranolol (Inderal)	Initial: 10-20mg PO BID MDD: 320mg/day	Tablet: 10mg, 20mg, 40mg, 60mg, 80mg Tablet (ER)*: 60mg, 80mg, 120mg, 160mg	• Consider if patient has liver cirrhosis to reduce portal hypertension • Titrate to resting HR of 55-60 beats/ min or as tolerated • Avoid if patient has comorbid lung disease	Y/N*

References

- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 571-9.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 233-235.
- Collucci, W. et al. Pharmacologic therapy of heart failure with reduced ejection fraction, UpToDate, literature review current through Nov. 2015.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3d: Ascites, accessed online Nov. 2015 at: http://www.cancer.gov/resources-for/hp/education/epeco/self-study/module-3/module-3d.pdf
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 93-96.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 533-34,575,863,874-5.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 87-90.
- Runyon, B. et al. Evaluation of adults with ascites, UpToDate, literature review current through Nov. 2015.
- Runyon, B. et al. Malignancy-related ascites, UpToDate, literature review current through Nov. 2015.
- Such, J. et al. Ascites in adults with cirrhosis: Initial therapy, UpToDate, literature review current through Nov. 2015.
- Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 256-257.

Asthenia / Fatigue

DEFINITION

Abnormal physical weakness or lack of energy.

CAUSES

- Disease states such as cancer, heart failure, lung disease, stroke and neuromuscular disease
- Concurrent conditions such as insomnia, depression, anemia, cachexia and anorexia
- Medications such as hypnotics, benzodiazepines, tricyclic antidepressants, antihistamines, or chemotherapy agents
- Deconditioning
- Poor diet/malnutrition

HOW TO RECOGNIZE SYMPTOM

- Complaints of fatigue, exhaustion, malaise or dizziness
- Easy tiring and reduced ability to maintain activity level
- Patient has difficulty in starting or performing an activity
- Decreased physical ability
- Lack of energy not relieved by rest

CLINICAL INSIGHTS

- Affects most people with chronic illnesses
- Treat underlying conditions (depression, malnutrition, anemia, infection, insomnia, pain)
- Decrease/discontinue, when possible, medications that may be contributing/ causing asthenia or fatigue
- Encourage methods to conserve energy, such as sitting down when possible to perform certain tasks such as cleaning, bathing or dressing.
- Fatigue due to opioid use is usually self-limiting and resolves within a few days
- Corticosteroid effects on fatigue appear to be short term, usually last 2-4 weeks. The risk benefit ratio of long term corticosteroid treatment should be weighed due the potential for adverse effects.
- Psychostimulants may reduce fatigue, promote a sense of well-being and improve symptoms of depression

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CORITOSTEROIDS				
Dexamethasone (Decadron)	Initial: 2-4mg PO QD MDD: not established for this indication	Oral solution: 0.5mg/5ml, 1mg/ml Tablet: 0.25mg, 0.5mg, 0.74mg, 1mg, 1.5mg, 2mg	• Most comprehensively studied corticosteroid in palliative care • Give dose in the morning to prevent insomnia • Beneficial where short term therapy is indicated • Start with low dose and monitor for efficacy weekly, can increase dose weekly upon reassessment • Also useful for bone pain, anorexia, or bronchospasm	Y
Prednisone	Initial: 10mg PO QD MDD: not established for this indication	Oral solution: 1mg/ml, 5mg/ml Tablet: 1mg, 2.5mg, 5mg, 10mg, 20mg, 50mg Tablet (DR)*: 1mg, 2mg, 5mg	• Effective doses vary • Give dose in the morning to prevent insomnia • Start with low dose and monitor for efficacy weekly • Titrate up by 2-5mg at weekly intervals if needed • Indicated when short term therapy may be beneficial (less than 6 weeks) • Also useful in treating bone pain, anorexia, or bronchospasm • Less expensive than dexamethasone	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
PSYCHOSTIMULANTS				
Armodafinil (Nuvigil)	Initial: 50-150mg PO QAM MDD: 250mg/day	Tablet: 50mg, 150mg, 200mg, 250mg	• Promotes wakefulness • Not approved for children 16 years and younger • Expensive	Y
Dextroamphetamine (Dexedrine)	Initial: 2.5mg QAM MDD: 20mg/day	Capsule (ER)*: 5mg,10mg,15mg Tablet: 5mg, 10mg	• Fast onset • Benefit for patients with limited life expectancy • Side effects include: insomnia, anorexia, anxiety, confusion, tachycardia	Y/N*
Methylphenidate (Ritalin, Concerta, Metadate, Daytrana)	Dose varies based on formulation MDD: 60mg/day	Capsule (CR)*: 10mg, 20mg, 30mg, 40mg, 50mg, 60mg Oral solution: 1mg/ml, 2mg/ml Tablet: 5mg, 10mg, 20mg Tablet (CR)*: 10mg, 18mg, 20mg, 27mg, 36mg, 54mg Transdermal patch: 10mg/9hr, 15mg/9hr, 20mg/9hr, 30mg/9hr	• Drug of choice for patients with prognosis < 2-4 weeks; onset is typically around 1 day • Do not crush extended release formulations • Contents of capsule may be opened and sprinkled into food • Take in morning (avoid doses after 12:00) • Side effects include: insomnia, anorexia, anxiety, confusion, tachycardia • Controlled release, patch, and liquid formulations are expensive	Y/N*
Modafinil (Provigil)	Initial: 100mg QAM MDD: 400mg/day	Tablet: 100mg, 200mg	• Promotes wakefulness • Studies are being done on fatigue related to chronic illnesses including cancer, ALS, MS, and HIV/AIDS • Less side effects than psychostimulants • Side effect is appetite suppression , headache, and irritability • Not approved for children 16 years and younger • Expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NUTRIENTS				
L-Carnitine (Carnitor)	Initial: 250-330mg PO TID MDD: 2,970mg/day oral, 50mg/kg IV	Capsule: 250mg, 300mg, 400mg Oral solution: 100mg/ml Solution for injection: 200mg/ml Tablet: 330mg, 500mg	• Consider if malnutrition is cause of fatigue • Theory that deficiency in carnitine may reduce energy production	N

References

- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 637-44.
- Bruera E, Yennurajalingam S, Arnold RM, Savarese DMF. Palliative Care: Overview of fatigue, weakness, and asthenia. UpToDate, 2015. Accessed online August 2015.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 170-174.
- Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000; 5:353-360.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3k: Fatigue, accessed online Nov. 2015 at: http://www.cancer.gov/resources-for/hp/education/epeco/self-study/module-3/module-3k-pdf
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 96.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 916, 1476.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Mücke M, Mochamat, Cuhls H, et al. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database of Systematic Reviews 2015, Issue 5
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 139,335.
- Radbruch L, Strasser F, Elsner F, et al. Fatigue in palliative care patients –and EAPC approach. Palliative Medicine 2008; 22:13-22.
- Ross DD, Alexander CS. Management of Common Symptoms in Terminally Ill Patients: Part 1. Fatigue, Anorexia, Cachexia, Nausea and Vomiting. AAFP, 2001: 64(5) 807-814.
- Yennurajalingam S, Bruera E. Palliative management of fatigue at the close of life: "it feels like my body is just worn out". JAMA 2007; 297:295-304.

Bleeding

DEFINITION

Blood loss from any cause, including low volume loss from the conjunctiva, epistaxis, and minor trauma.

CAUSES

- Trauma / breaks in the skin
- Medications such as anticoagulants, antiplatelets and NSAIDs
- Advanced cancers such as head and neck, lung, acute leukemia
- Liver or kidney disease
- Thrombocytopenia
- Dehydration

HOW TO RECOGNIZE SYMPTOM

- Bleeding may be visible (ex: urine, sputum, nose or surface of skin) or unseen (occult bleeding)
- Signs and symptoms of occult bleeding include fatigue, weakness, paleness, hypotension, tachycardia, or altered mental status
- Blood in the feces may appear black and tarry
- Blood in vomitus may have a coffee ground-like appearance

CLINICAL INSIGHTS

- The risks and benefits of medications that increase bleeding risk (ex: anticoagulants, antiplatelets and NSAIDs) should frequently be reviewed
- Drug therapy to control bleeding can be local or systemic
- A small bleed may precede a more severe bleed
- Identify patients at risk for a catastrophic bleed and develop a preparatory care plan
- Catastrophic bleeding events include carotid blowout syndrome, GI or variceal bleed, intractable hematuria and massive terminal hemoptysis.
  - » When bleeding cannot be controlled, supportive measures to mask the bleed and administration of medications such as anxiolytics and/or opioid analgesics to minimize distress may be warranted.
- Oral thrombolytic inhibitors, such as tranexamic acid or aminocaproic acid, are expensive, but may be used for bleeding at a number of different sites in a number of different preparations.
- 5α-reductase inhibitors should be continued if urinary bleeding due to prostate cancer
- Prednisone 40mg PO QD is an option for upper G.I. bleed due to radiation induced gastritis
- Dexamethasone 2-4mg PO/IV/SQ QD is an option for hemoptysis
- Topical compounds such as Moh's paste are potentially useful for controlling surface bleeding

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
VASOCONSTRICTORS				
Epinephrine (Adrenalin)	Initial (epistaxis): soak ribbon gauze with solution, then pack nasal cavity Initial (surface bleeding): soak gauze and apply with pressure x 10min Initial (oropharynx bleeding): 5ml mixed with 5ml normal saline nebulized QID PRN Initial (hemoptysis): 1ml mixed with 4ml normal saline nebulized QID PRN	Solution for injection: 1mg/ml	• May be used for bleeding due to vasoconstrictive properties • Rebound bleeding is a potential adverse effect	-
Naphazoline (Clear Eyes)	Ophthalmic: 1-2 drops into each eye	Ophthalmic solution: 0.012%, 0.025%, 0.1%	• For conjunctival bleeding	-
Oxymetazoline (Afrin)	Initial (epistaxis): 2-3 sprays each nostril BID PRN Initial (surface bleeding): soak gauze and apply with pressure x 10min	Nasal spray: 0.05%	• May be used for bleeding due to vasoconstrictive properties • Intranasal use for more than 3 consecutive days may result in dependence or rebound congestion with discontinuation • Rebound bleeding is a potential adverse effect	-
Phenylephrine (Neo-synephrine)	Initial (epistaxis): 2-3 sprays or drops in each nostril Q4 hours PRN Initial (surface bleeding): soak gauze and apply with pressure x 10min	Nasal spray: 0.25%, 0.5%, 1%	• May be used for bleeding due to vasoconstrictive properties • Intranasal use for more than 3 consecutive days may result in dependence or rebound congestion with discontinuation • Rebound bleeding is a potential adverse effect	-
Vasopressin (Pitressin)	Initial (hemoptysis): 5 units in 2ml normal saline nebulized BID-TID	Solution for injection: 20units/ml	• Inexpensive	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ORAL THROMBOLYTIC INHIBITORS				
Aminocaproic Acid (Amicar)	Initial (systemic, acute): 5grams PO/IV STAT, then 1-1.5 grams Q hour until stopped Initial (systemic, chronic) 1-4 grams PO Q4-8 hours Initial (bladder irrigation): 200mg in 1L normal saline infused continually until 24 hours after bleeding stopped	Solution for injection: 250mg/ml Syrup: 250mg/ml Tablet: 500mg, 1,000mg	• Potential option for controlling bleeding at a number of different sites • Caution should be used if considering for urinary bleeding as existing clot degradation will be slowed, potentially leading to obstruction • Therapy is typically continued for 7-10 days after bleeding stops • Reduce dose in patients w/ renal impairment • Less potent than tranexamic acid • Expensive	Y
Tranexamic Acid (Lysteda, Cyklokapron)	Initial (systemic): 1-1.5 grams PO BID-QID Initial (oropharynx): rinse mouth BID with mouthwash prepared by 5 grams of solution for injection plus 50ml warm water Initial (rectal): give enema prepared with 5 grams of solution for injection plus 50ml warm water BID Initial (vaginal): 1 tablet crushed and mixed with KY jelly applied vaginally OR soak gauze with 5ml of solution for injection and apply vaginally Initial (nebulized): 5ml (500mg) via SVN TID-QID; alternatively 10ml (1,000mg) via continuous SVN over 30-45 minutes as single treatment	Solution for injection: 100mg/ml Tablet: 650mg	• Potential option for controlling bleeding at a number of different sites • Caution should be used if considering for urinary bleeding as existing clot degradation will be slowed, potentially leading to obstruction • Therapy is typically continued for 7-10 days after bleeding stops • Reduce dose in patients w/ renal impairment • 10 times more potent than aminocaproic acid • For rectal bleeding, may reduce enema frequency to 3 times weekly once controlled • Expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIDOTES TO ANTICOAGULANTS				
Protamine Sulfate	Initial (heparin reversal): 1mg per unit of heparin; max 50mg per dose Initial (LMWH reversal, off label): 0.5-1mg per mg enoxaparin or 1mg per 100 anti-Xa units of dalteparin or tinzaparin	Solution for injection: 10mg/ml	• For reversal of continuous IV infusion of heparin, consider only the heparin administered in the previous 2-2.5 hours • Anti-Xa (factor ten) activity is not completely reversed	-
Vitamin K (Mephyton)	Initial: 2.5-10mg PO/IV QD, repeated if needed	Solution for injection: 10mg/ml Tablet: 5mg	• SQ less effective than other routes • IV route may be preferred for severe bleeds • Oral absorption significantly reduced in patients with liver disease • Expensive	Y
BARRIER FORMING				
Sucralfate (Carafate)	Initial (surface bleeding): 1-2 tablets crushed into water soluble gel applied QD-BID Initial (oropharynx bleeding): 2,000mg of suspension PO BID Initial (upper G.I. bleeding): 1,000mg PO QID or 2,000mg PO BID Initial (rectal bleeding): 2,000mg of suspension by enema BID Initial (anal bleeding): 1-2 tablets crushed into water soluble gel applied BID	Oral suspension (brand only): 1,000mg/10ml Tablet: 1,000mg	• Forms physical barrier to slow bleeding • Suspension more expensive than tablets	Y
CAUTERIZING AGENTS				
Silver Nitrate (Arzol)	Initial: 1 stick applicator	Stick: 25%, 75%	• For chemical cauterization on mucous membranes and other moist skin surfaces only on area to be treated that are bleeding • Can moisten applicator with water immediately before use on dry skin • Discomfort with administration	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER				
Octreotide (Sandostatin)	Initial: 50mcg SQ BID or 100-250mcg IV bolus followed by 25mcg/hr infusion	Solution for injection: 50mcg/ml,100mcg/ml, 200mcg/ml,500mcg/ml	• Lack of consensus dose for this indication • Expensive	-
SEDATIVE HYPNOTICS FOR USE DURING CATASTROPHIC BLEEDING				
Diazepam (Valium)	Initial: 10mg IV/PR	Solution for injection: 5m/ml Suppository: 10mg (compound)	• IV route preferred due to near immediate onset	-
Lorazepam (Ativan)	Initial: 4mg IV/SQ/SL	Oral solution: 2mg/ml Solution for injection: 2mg/ml	• IV route preferred due to rapid onset • Onset of action is ~5min with SL route	-
Midazolam (Versed)	Initial: 5-10mg IV/SQ/ buccal	Solution for injection: 5mg/ml	• Drug of choice for anxiolysis during catastrophic bleed • Amnesic effect beneficial if bleed is non-fatal • IV route preferred due to rapid onset	-

References

- Amarapurkar, P. et al. Management of Coagulopathy in Patients with Decompensated Liver Cirrhosis, International Journal of Hepatology, Vol. 2011, Article ID 695470, 5 pages, 2011. doi:10.4061/2011/695470.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 808-16.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 288-290.
- Dean, A., et al. Fibrinolytic Inhibitors for Cancer-Associated Bleeding Problems, Journal of Pain and Symptom Management. 1997; 13:20-24.
- Fine, P. The Hospice Companion, 2nd ed. 2012., pp. 66-72
- Hankerson, M. et al. Nebulized tranexamic acid as a noninvasive therapy for cancer-related hemoptysis, J Pal Med, 2015; 18(12): 1060.
- Hanks, et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 963-971.
- Harris, D., et al. Management of Terminal Hemorrhage in Patients with Advanced Cancer: A Systemic Literature Review, Journal of Pain and Symptom Management, 2009; 38:913-927.
- Hull, R. et al., Correcting excess anticoagulation after warfarin, UpToDate database, accessed online March 2015.
- Hulme, B. et al., Guidelines on the management of bleeding for palliative care patients with cancer, accessed online March 2015 [http://www.palliativedrugs.com/download/090331_Final_bleeding_guideline.pdf]
- Kakimoto, M., et al. A Chemical Hemostatic Technique for Bleeding from Malignant Wounds, Journal of Palliative Medicine, 2010; 13:11-13.
- Kalmadi, S. et al. Epsilon Aminocaproic Acid Reduces Transfusion Requirements in Patients With Thrombocytopenic Hemorrhage, Cancer, 2006; 107:136-140.
- Kratz, A. et al., Controlling bleeding from superficial wounds by the use of topical alpha adrenoreceptor agonists spray – A randomized, masked, controlled study, International Journal of the Care of the Injured, 2004; 25:1096-1101.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Pereira, J., et al. Management of Bleeding in Patients with Advanced Cancer, The Oncologist, 2004;9:561-570.
- Recka, K., et al., Management of Bleeding Associated with Malignant Wounds, Journal of Palliative Medicine, 2012; 15:952-954.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 93,333.
- Roberts, S., et al., Palliative Use of Aminocaproic Acid to Control Upper Gastrointestinal Bleeding, Journal of Pain and Symptom Management, 2010; 40:e1-e3.
- Solomonov, A. et al. Pulmonary hemorrhage: a novel mode of therapy, Resp Med, 2009; 103: 1196.
- Spiess, J., et al. Can I Stop the Warfarin? A Review of the Risks and Benefits of Discontinuing Anticoagulation. Journal of Palliative Medicine 2009 Vol. 12, No. 1.
- Yanazume, Y. et al. Clinical Usefulness of Moh's Paste for Genital Bleeding from the Uterine Cervix or Vaginal Stump in Gynecologic Cancer, Journal of Palliative Medicine, 2013; Vol 16 No.2.

Bronchospasm

DEFINITION

Sudden contraction of the bronchi in the lungs in response to an irritant or due to exacerbation of lung disease resulting in narrowing of the airway.

CAUSES

- Lung diseases, such as COPD (Emphysema / Chronic bronchitis), asthma or pneumonia
- Airborne irritants, such as smoke, pollen or dust
- Medications, such as non-cardioselective beta-blockers (nadolol, propranolol and carvedilol), high dose cardioselective beta-blockers (selectivity is overcome), acetylcholinesterase inhibitors or NSAIDs
- Inhalation of medications not intended for pulmonary administration (ex: inhaled morphine solution for injection)
- Particulates in dry powder inhalers (DPIs)
- Anaphylaxis / allergic reaction
- Overcooling / drying of airways
- Hyperventilation

HOW TO RECOGNIZE SYMPTOM

- Coughing and/or wheezing
- Dyspnea

CLINICAL INSIGHTS

- If possible, avoid or discontinue medications that may cause drug-induced bronchospasm
- The nebulized route of administration is preferred over metered dose inhalers (MDIs) or dry powder inhalers (DPIs) for patients with severe lung disease or impaired cognition/coordination to ensure optimal drug delivery and symptom control.
- If an MDI must be used, a spacer can improve drug delivery and symptom control; however, spacers cannot be used with DPIs.
- Duplicate therapy within the same therapeutic class is not recommended and is associated with increased adverse effects and unnecessary drug spend.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Albuterol (Ventolin, Proventil, ProAir)	Initial (MDI): 1-2 puffs (90-180) mcg every 4 hours PRN Initial (nebulized): 1 SVN Q4 hours PRN MDD (MDI): 12 puffs/day MDD (nebulized): 6 nebs/day	Concentrated solution for nebulization: 5mg/ml Metered dose inhaler (MDI): 90mcg/actuation Oral solution: 2mg/5ml Solution for nebulization: 0.63mg/3ml, 1.25mg/3ml, 2.5mg/3ml Tablet: 2mg, 4mg Tablet (ER)*: 4mg, 8mg	• Agent of choice for treatment of acute bronchospasm • Dose-related tachycardia, CNS stimulation/excitation • Anecdotally, the maximum daily dose is occasionally exceeded in the hospice setting	Y/N*
Albuterol/Ipratropium (Duoneb, Combivent)	Initial (Respimat MDI): 1 puff QID Initial (nebulized): 1 SVN QID MDD (Respimat MDI): 4 puffs/day MDD (nebulized): 6 nebs/day	Metered dose inhaler (Respimat): 20mcg ipratropium/100mcg albuterol/actuation Solution for nebulization: 0.5mg ipratropium/ 2.5mg albuterol/ 3ml	• Used for acute management with greater efficacy than either agent alone • Combination product can be used for both treatment and prevention • Combivent Respimat replaced Combivent Aerosol (Removed from US market in Dec. 2013) • Helpful in COPD-related bronchospasm • Dose-related tachycardia, CNS stimulation/excitation • Can have additive adverse anticholinergic adverse effects when used with other anticholinergics	-
Beclomethasone Dipropionate (QVAR)	Initial: 40-80mcg BID MDD: 320mcg/day	Metered dose inhaler (MDI): 40mcg/actuation, 80mcg/actuation	• Not indicated for acute exacerbations • Can cause edema, exacerbating CHF or hypertension • Can contribute to oral candidiasis, rinse mouth with water to avoid	-
Budesonide-Formoterol (Symbicort)	Initial: 2 inhalations of 80/4.5mcg strength BID MDD: 640/18mcg/day	Metered dose inhaler (MDI): 80/4.5mcg, 160/4.5mcg/ actuation	• Not indicated for acute exacerbations • Do not use or initiate in patients with acutely deteriorating asthma/COPD • Can contribute to oral candidiasis, rinse mouth with water to avoid • Dose-related tachycardia, CNS stimulation/excitation • Patient must have sufficient inspiratory force to effectively use dosage form	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Cromolyn Sodium (Gastrocrom)	Initial: 20mg SVN QID MDD: 80mg/day	Solution for nebulization: 20mg/2ml	• Not indicated for acute exacerbations • Has an unpleasant taste and can contribute to stomatitis	-
Fluticasone Propionate HFA (Flovent)	Initial (MDI): 88-220mcg BID Initial (DPI): 100mcg BID MDD (MDI): 880mcg/day MDD (DPI): 1,000mcg/day	Dry powder inhaler (DPI): 100mcg/actuation, 250mcg/actuation Metered dose inhaler (MDI): 44mcg/actuation, 110mcg/actuation, 220mcg/actuation	• Not indicated for acute exacerbations • Can cause edema, exacerbating CHF or hypertension • Can contribute to oral candidiasis, rinse mouth with water to avoid	-
Fluticasone-Salmeterol (Advair)	Initial (DPI): one inhalation BID of 250-50mcg strength Initial (MDI): 2 inhalations of 115-21mcg strength MDD (DPI): 2 inhalations/day MDD (MDI): 4 inhalations/day	Dry powder inhaler (DPI): 100-50mcg, 250-50mcg, 500-50mcg Metered dose inahler (MDI): 45-21mcg, 115-21mcg, 230-21mcg	• Not indicated for acute exacerbations • Do not use or initiate in patients with acutely deteriorating asthma/COPD • Can contribute to oral candidiasis, rinse mouth with water to avoid • Dose-related tachycardia, CNS stimulation/excitation • Patient must have sufficient inspiratory force to effectively use dry powder inhaler	-
Ipratropium Bromide (Atrovent)	Initial (MDI): 2 puffs QID Initial (nebulized):1 SVN QID MDD (MDI): 12 puffs/day MDD (nebs): 6 nebs/day	Metered dose inhaler (MDI): 17mcg/actuation Solution for nebulization: 0.5mg/2.5ml (0.02%)	• Not indicated for acute exacerbations • Can have additive adverse anticholinergic adverse effects when used with other anticholinergics	-
Levalbuterol (Xopenex)	Initial (MDI): 90mcg Q 4-6hr routinely or PRN Initial (nebulized): 0.63mg SVN TID routinely or PRN MDD (MDI): 12 inhalations/day MDD (nebulized): 3 nebs/day	Metered dose inhaler (MDI): 45mcg/actuation Solution for nebulization: 0.63mg/3ml, 1.25mg/3ml	• Indicated for treatment of acute bronchospasm and prophylaxis • Dose-related tachycardia, CNS stimulation/excitation • Expensive	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Prednisone (Sterapred)	Initial (acute): 40-60mg as a single dose or 2 divided doses for 3-10 days MDD: 60mg/day	Oral solution: 1mg/ml, 5mg/ml Tablet: 1mg, 2.5mg, 5mg, 10mg, 20mg, 50mg	• Administer with food to minimize GI irritation • Administer in morning to coincide with normal cortisol secretion and minimize insomnia • Use caution in hepatic impairment as it is hepatically metabolized • Can cause edema, exacerbating CHF or hypertension	Y
Salmeterol Xinafoate (Serevent)	Initial: 50mcg Q12 hr MDD: 100mcg/day	Dry powder inhaler (DPI): 50mcg/dose	• Not indicated for acute exacerbations • Dose-related tachycardia, CNS stimulation/excitation • Patient must have sufficient inspiratory force to effectively use dosage form	-
Theophylline (Theo-24, Uniphyl)	Initial (Oral solution): 300mg / day in 3-4 divided doses Initial (12-hour ER): 300-400mg/day divided BID Initial (24-hour ER): 300-400mg QD MDD (all forms): 600mg/day (400mg/day if > 60 years old)	Capsule (ER, 24hr): 100mg, 200mg, 300mg, 400mg Oral solution: 80mg/15ml Tablet (ER, 24hr): 400mg, 600mg Tablet (ER, 12hr): 100mg, 200mg, 300mg, 450mg	• Indicated for maintenance therapy of asthma or COPD and bronchospasm prophylaxis • Titrate to serum concentration 5-15mcg/ml; higher doses may be used if serum levels indicate need • Should be taken with a full glass of water • Capsules may be opened and contents mixed with soft foods; do not chew or crush medication beads • Theophylline toxicity may present as persistent nausea/vomiting, seizure, arrhythmia	N
Tiotropium Bromide Monohydrate (Spiriva)	Initial: 18mcg Q24 hr (the contents of one capsule should be inhaled with two separate inhalations) MDD: 18mcg/day	Dry powder inhaler (DPI): 18mcg/capsule	• Not indicated for acute exacerbations • Capsule is used in the Handihaler inhaler, not swallowed • Patient must have sufficient inspiratory force to effectively use dry powder inhaler • Dry powder inhalers cannot be used with spacers or other devices	-

References

- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 938-9.
- Fagan, N. et al. Therapeutic update on drug-induced pulmonary disorders, USpharmacist.com, accessed online Nov. 2015 at: http://www.uspharmacist.com/content/d/feature/c/29051/
- Jarvis, S. et al. Inhaled therapy in elderly COPD patients; time for re-evaluation? Age and Ageing, 2007;36:213-18.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Malipatil, V. et al. Management of older people with chronic obstructive pulmonary disease, Journal of Pharmacy Practice and Research, 2009, Vol.39, No.4.
- Melani, A. et al. Inhaler mishandling remains common in real life and is associated with reduced disease control, Respiratory Medicine, (2011)105,930-38.
- Nobles, J. et al. Potential Problems and Solutions with Inhaler Use in Elderly COPD Patients, The Consultant Pharmacist, 2014, Vol.29, No. 11.
- Puhan, M. et al. Inhaled drugs to reduce exacerbations in patients with chronic obstructive pulmonary disease: a network meta-analysis, BMC Medicine, 2009; 7:2.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 341.
- Rootmensen, G. et al. Predictors of Incorrect Inhalation Technique in Patients with Asthma or COPD, Journal of Aerosol Medicine and Pulmonary Drug Delivery, 2010, Vol. 23, No. 5.
- Vanderman, A. et al. Inhaler misuse in an older adult population, The Consultant Pharmacist, 2015, Vol. 30, No.2.
- Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 1030-1040.

Constipation

DEFINITION

Constipation is a highly prevalent and distressing symptom in patients with advanced, progressive, chronic illness where stool frequency occurs less often than patients' normal patterns (commonly defined as less than 3 bowel movements per week) with hard stools that are dry and difficult to pass.

CAUSES

- Gastrointestinal disorders or blockage:
  - Tumors
  - Stricture
  - Rectal prolapse
  - Hemorrhoids
  - Irritable bowel syndrome
- Neurological disorders:
  - Parkinson disease
  - ALS
  - Multiple sclerosis
  - Cerebrovascular disease
  - Spinal cord lesions
  - Diabetic autonomic neuropathy
- Medications:
  - Opioids
  - Anticholinergics
  - Tricyclic antidepressants
  - Anti-Parkinson agents
  - Antihistamines
  - Urinary antispasmodics
  - Anticonvulsants
  - Antipsychotics
  - Diuretics
  - NSAIDs
  - Calcium containing antacids / supplements
  - Iron
  - Calcium channel blockers
  - Clonidine
  - Excessive use of antidiarrheal medications
  - Cholestyramine
  - Serotonin (5-HT3) antagonists such as ondansetron
- Inadequate fluid intake
- Excessive fiber intake without adequate hydration
- Lack of privacy
- Decreased mobility / physical activity
- Hard stools / fear of pain exacerbation due to straining during bowel movement
- Radiation fibrosis
- Dietary changes
- Hypothyroidism
- Uremia
- Electrolyte disturbances such as hypercalcemia and hypokalemia
- Anorexia

HOW TO RECOGNIZE SYMPTOM

- Reduced stool frequency
- Increased straining to pass a bowel movement
- Passage of small, hard stools
- Feeling that bowels have not emptied completely after a bowel movement
- Abdominal pain / distension

CLINICAL INSIGHTS

- If possible, attempt to remove precipitating causes such as medications that may worsen constipation
- Onset of laxative action varies by choice of laxative and presence of concurrent opioid use and can take up to 48 hours to produce a bowel movement
- Bowel care should be initiated at the same time as opioids to prevent opioid-induced constipation
- Senna is the drug of choice for treatment / prevention of opioid-induced constipation
- As a rule of thumb, 1 tablet of senna for every 15mg of oral morphine or equivalent can be used, although opioid induced constipation does not always worsen as the opioid is titrated
- Docusate is not a laxative and will not prevent constipation, with the possible exception of doses more than 400mg per day, which may act as a stimulant laxative
- Use caution with osmotic laxatives in dehydrated patients because they draw water into the bowel and can worsen dehydration
- Magnesium containing laxatives are contraindicated in patients with kidney disease due to the potential for adverse effects due to magnesium accumulation

- Rectal pain / hemorrhoids that commonly occurs due to straining with bowel movements can typically be successfully treated with medications such as Preparation H or topical hydrocortisone.
- Duplicate therapy within the same therapeutic class should typically be avoided
- Senna and bisacodyl are prodrugs that require conversion to their active forms in the G.I. tract. This conversion depends on the presence of certain bacterial flora and may be absent due to inter-individual differences in bacterial flora, resulting in ineffective laxation.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
STIMULANT LAXATIVES				
Bisacodyl (Dulcolax)	Initial (tablets): 1-8 tablets PO QD PRN Initial (suppository): 1 suppository PR QD PRN MDD (tablets): 40mg/day MDD (suppository): 20mg/day	Suppository: 10mg Tablet*: 5mg	• Suppository onset of action 15 minutes to 2 hours. • Tablet onset of action 6 to 10 hours • Stimulant laxative • Can be used daily or PRN	Y/N*
Senna (Ex-Lax)	Initial: 1-8 tablets PO divided QD-BID PRN MDD: 8 tablets or 40ml/day	Oral solution: 8.8mg/5ml Tablet: 8.6mg sennosides	• Onset of action 6-12 hours • Drug of choice for opioid induced constipation • The typical maximum daily dose is occasionally exceeded in the hospice setting	Y
Senna/Docusate Sodium (Senna-S)	Initial: 1-2 tablets PO daily to BID MDD: 8 tablets/day	Tablet: Docusate 50mg/ Senna 8.6mg	• See individual drugs for onset of action • Stimulant laxative + stool softener combo • May crush, although tablets have a poor taste when crushed	Y
OSMOTIC LAXATIVES				
Magnesium Citrate (Citroma)	Initial: ½ to 1 bottle (150-300ml) PO PRN MDD: 1 bottle/day	Oral solution: 1.745g/30ml	• Onset of action 30 minutes to 6 hours • Contraindicated w/ renal impairment • Avoid in patients with heart failure due to high salt content and potential to worsen fluid overload • May be given as single or divided dose • Reported to taste better when cold • Keep chilled in refrigerator after opening	-
Magnesium Hydroxide (Milk of Magnesia)	Initial (suspension): 30-60ml QD Initial (tablet): 1-8 tablets once daily or in divided doses MDD (suspension): 60ml/day MDD (tablet): 8 tablets/day	Chewable tablet: 311mg Oral suspension 400mg/5ml, 800mg/5ml	• Onset of action in 30 minutes to 3 hours • Contraindicated w/ renal impairment • Consider milk of magnesia if senna in combination with docusate is ineffective *(Continued on next page)*	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OSMOTIC LAXATIVES (CONTINUED)				
Glycerin Suppositories (Fleet glycerin, Pedia-Lax)	Initial: 1 suppository PR daily to BID PRN MDD: 2 suppositories	Suppository: 1.2gm, 2gm, 2.1gm	• Onset of action 15 min. to 1 hr • To be used as needed for hard, dry stool • May cause "fatty" appearing stool	-
Lactulose (Enulose)	Initial: 15-30ml (10-20g) PO QD MDD: 240ml/day	Syrup: 10g/15ml	• Onset of action up to 24-48 hours • Laxative of choice if liver failure is present • Titrate to produce 3 to 4 soft stools per day, avoiding diarrhea for hepatic encephalopathy • Does not increase blood glucose • Associated with more cramping / bloating than other osmotic laxatives	-
Magnesium Oxide (Uro-mag, Maox)	Initial: 1-8 tablets PO QHS or in divided doses MDD: 8 tablets/day	Tablet: 400mg	• Contraindicated w/ renal impairment	Y
Polyethylene Glycol (Miralax)	Initial: 17g (one capful) in 8oz of fluid daily MDD: 34g/day	Powder	• Onset of action 24-96 hours • Patient must be adequately hydrated • May not be suitable for patients with volume intolerance • Preferred osmotic laxative in patients with renal impairment • Best tolerated osmotic laxative	-
Sodium Phosphates (Fleet Enema)	Initial: 1 enema PR x 1 dose MDD: 2 enemas /day	Enema: 5.6gm/dose	• Onset of action 2 to 15 min. • Use with caution in patients w/ renal impairment • Avoid in patients with heart failure due to high salt content and potential to worsen fluid overload	-
Sorbitol	Initial: 15-60ml PO divided QD-QID MDD: 240ml/day	Oral solution: 70%	• Excessively sweet taste • Does not increase blood glucose	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
LUBRICANT LAXATIVES				
Mineral Oil (Fleet Oil)	Initial (oral): 15-45 ml PO QHS or in divided doses Initial (enema): 1 enema PR as directed MDD (oral): 45ml/day MDD (enema): 1 enema/day	Enema Oral oil	• Onset of action 6-8 hours (oral) or 2-15min. (rectal) • Lubricant laxative • Avoid oral administration if aspiration risk • Taste may be improved if refrigerated or by mixed with flavored juice	-
PROKINETIC AGENTS				
Azithromycin (Zithromax)	Initial: 250mg daily MDD: 500mg/day	Suspension: 100mg/5ml, 200mg/5ml Tablet: 250mg, 500mg	• Less studied than erythromycin, but demonstrates comparable efficacy • Advantages over erythromycin include: less expensive, fewer drug interactions, once daily dosing, fewer GI side effects, lower risk of QTc-interval prolongation	Y
Erythromycin (EES, Eryped)	Initial: 250mg PO TID MDD: 1,500mg/day	Oral suspension: 200mg/5ml Tablet: 250mg, 500mg	• Consider for N/V caused by delayed gastric emptying • Effective in about ½ of patients • Can be used for constipation • Use oral base preparations (not enteric coated) • Monitor for adverse effects including cramping / colicky pain • Expensive	Y
Metoclopramide (Reglan)	Initial: 5mg PO TID AC MDD: 40mg/day	Oral solution: 1mg/ml Solution for injection: 5mg/ml Tablet: 5mg, 10mg	• May also benefit partial bowel obstruction or GERD symptoms • Give doses before meals and at bedtime • Monitor for extrapyramidal symptoms	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OPIOID ANTAGONISTS				
Methylnaltrexone (Relistor)	Initial (OIC in patients with chronic non-cancer pain): 12mg SQ QD Initial (OIC in patients with advanced illness): - <38kg: 0.15mg/kg SQ QOD - 38-62kg: 8mg SQ QOD - 62-114kg: 12mg SQ QOD - >114kg: 0.15mg/kg SQ QOD MDD: same as initial dose QD	Solution for injection: 8mg/0.4ml, 12mg/0.6ml	• Onset of action 30-60min in responding patients • Not first line therapy; reserve use for when other laxatives, including stimulant types, have failed • For opioid induced constipation (OIC) only • Round weight based doses to nearest 0.1ml of volume • Expensive	-
Naloxegol (Movantik)	Initial: 25mg PO QD; 12.5mg PO QD if CrCl < 60 MDD: 25mg/day	Tablet: 12.5mg, 25mg	• Not first line therapy; reserve use for when other laxatives, including stimulant types, have failed • For opioid induced constipation (OIC) only • Recommended to discontinue all maintenance laxatives before initiating therapy; may re-introduce after 3 days if needed • Alteration of the existing opioid regimen is not required • Avoid if patient has severe liver disease • Expensive	N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
STOOL SOFTENERS				
Docusate Calcium (Surfak)	Initial: 240mg PO QD MDD: 720mg/day div. BID	Capsule: 240mg	• Onset of action 12-72 hours • Typically does not provide laxative effect, but may act as a stimulant laxative at doses > 400mg per day • Requires adequate fluid intake for efficacy May be given as single or divided dose • Possibly preferred if sodium restriction	N
Docusate Sodium (Colace)	Initial: 100mg PO BID MDD: 800mg/day	Capsule*: 50mg, 100mg, 250mg Oral solution: 50mg/5ml Tablet: 100mg	• Onset of action 12-72 hours • Typically does not provide laxative effect, but may act as a stimulant laxative at doses > 400mg per day • Requires adequate fluid intake for efficacy • Oral liquid has poor taste and may cause nausea	Y/N*
OTHER AGENTS COMMONLY USED FOR CHRONIC IDIOPATHIC CONSTIPATION (CIC) OR CONSTIPATION PREDOMINANT IRRITABLE BOWEL SYNDROME (IBS-C)				
Linaclotide (Linzess)	Initial: 145mcg PO QD for CIC; 290mcg PO QD for IBS-C MDD: 290mcg/day	Capsule: 145mcg, 290mcg	• Give 30min prior to 1st meal of the day on empty stomach • Not commonly used in the hospice setting • Expensive	N
Lubiprostone (Amitiza)	Initial: 24mcg PO BID for CIC or opioid induced constipation; 8mcg PO BID for females with IBS-C	Capsule: 8mcg, 24mcg	• Also indicated for opioid-induced constipation • Take with food and water • Not commonly used in the hospice setting • Syncope and hypotension have been reported in post-marketing surveillance • Ineffective in patients maintained on methadone • Expensive	N

References

- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 544-60.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 239-243.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3f: constipation, accessed online Nov. 2015 at: http://www.ipcrc.net/epco/EPEC-O%20M03a-q%20Symptoms/EPEC-O%20M03f%20Constipation/EPEC-O%20M03f%20Constipation%20PH.pdf
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 77.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 231, 236, 833-843, 1271.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Rao, S. et al. Constipation in the older adult, UpToDate, literature review current through Nov. 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 107.
- Wald, A. et al. Management of chronic constipation in adults, UpToDate, literature review current through Nov. 2015.

Cough

DEFINITION

A rapid expulsion of air from the lungs meant to remove fluid, mucus, or other materials from the lungs or airways.

CAUSES

- Malignant illness:
  - » Lung cancer / metastases
  - » Radiation or chemotherapy induced fibrosis
- Non-malignant chronic illness:
  - » COPD
  - » Congestive heart failure
  - » GERD
- Environmental / physical irritants
  - » Post-nasal drip due to allergies or infection
  - » Respiratory irritants such as dust, pollen or dander
  - » Stomach acid entering oropharynx due to GERD
  - » Excessive secretions
  - » Aspiration
  - » Cold weather
- Inflammation
  - » Laryngitis
  - » Sinusitis
- Infection
  - » Viral
    - ° Common cold
    - ° Pneumonia
    - ° Influenza
- Bacterial infections
  - ° Pneumonia
  - ° Pertussis (whooping cough)
- Acute pulmonary complications
  - » Pleural effusion
  - » Pulmonary embolism
- Medications
  - » ACE-inhibitors (less commonly ARBs)
  - » IV fentanyl

HOW TO RECOGNIZE SYMPTOM

- Direct observation
- Productive cough will have sputum in expectorate

CLINICAL INSIGHTS

- If possible, address reversible causes including discontinuation of medications that may cause cough
- Scheduled, rather than as-needed treatments are recommended for chronic, frequent cough
- Cough can be broadly divided into two categories: productive / wet cough and dry cough
- Because coughing is how mucus is cleared in a patient with a productive/wet cough, it is not recommended to treat this type of cough with antitussives unless symptoms are unbearable to the patient.
- Drug therapy should be targeted towards improving specific symptoms / characteristics of cough:
  - » Mucolytics can improve the clearing of thick pulmonary secretions
  - » Cough suppressants / antitussives suppress cough
  - » Antihistamines can be used to dry wet cough and reduce post nasal drip
  - » Multidrug combination products should only be used if all components are directed at specific symptoms
- Non-antitussive / expectorant adjuvants may be beneficial situationally, depending on the cause of cough, such as:
  - » Nebulized bronchodilators for dyspnea / cough due to exacerbation of pulmonary disease
  - » Acid suppressive therapy with PPIs or H2RAs for cough due to GERD
  - » Antibiotics for cough due to respiratory infection if consistent with goals of care / prognosis
  - » Diuretics for cough due to edema (ex: CHF)
  - » Corticosteroids if suspected inflammatory component to cough
- All opioids are antitussive; rather than adding an additional antitussive, consider titration of an existing opioid regimen if present

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTITUSSIVES / COUGH SUPPRESSANTS				
Benzonatate (Tessalon Perles)	Initial: 100mg PO TID MDD: 600mg/day	Capsule: 100mg, 200mg	• Anesthetic cough suppressant for non-productive cough • Must be swallowed whole	N
Dextromethorphan (Robitussin Cough Gels, Elixsure, Little Colds Cough Formula, Scot-Tussin Cf, Triaminic La, Hold, Trocal, Delsym)	Initial (IR dosage forms): 10-20mg Q4 hours PRN or 30mg Q6-8 hours PRN Initial (ER suspension): 30-60mg BID MDD (all forms): 120mg/day	Capsule: 15mg Lozenge: 5mg, 7.5mg Oral disintegrating strip: 7.5mg Oral solution: 5mg/5ml, 7.5mg/ml, 7.5mg/5ml, 10mg/5 ml,15mg/5ml, 20mg/15ml Oral suspension (ER): 30mg/5ml	• First line therapy for dry cough	Y
Hydrocodone/ Homatropine (Hycodan, Hydromet, Tussigon)	Initial: 1 tablet or 5ml PO Q4-6 hours PRN MDD: 6tabs or 30ml/ day	Syrup: 5mg hydrocodone/ 1.5mg homatropine / 5ml Tablet: 5mg hydrocodone bitartrate/ 1.5mg homatropine	• CII controlled substance • Homatropine is an anticholinergic agent present in subtherapeutic amount to deter abuse	-
Short-Acting Opioid Agonists	Initial: varies depending on opioid MDD: no ceiling dose for opioids	Varies depending on opioid	• All opioids possess antitussive properties	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
EXPECTORANTS				
Acetylcysteine (Mucomyst)	Initial (nebulized): 3-5ml of 20% or 6-10ml of 10% nebulized TID-QID Initial (oral): 200mg BID-TID, 300mg BID or 600mg QD MDD (nebulized): 120ml of 20% or 240ml of 10% per day MDD (oral): 1,200mg/day	Solution for injection: 10% (100mg/ml), 20% (200mg/ml)	• Not first line therapy • Oral route is off-label • When giving via nebulizer, give with or after a bronchodilator to optimize effect • When giving via oral route, may reduce frequency to 3x per week for maintenance • Complex administration requires drawing up dose in syringe and may not be possible for some patients • Expensive	-
Guaifenesin (Robitussin, Mucinex, Mucinex Max)	Initial (solution, IR tablet)200-400mg PO q4h PRN Initial (ER tablet) 1 tablet PO q12h MDD (all forms): 2,400mg/day	Syrup: 100mg/5ml Tablet: 200mg, 400mg Tablet (ER)*: 600mg,1,200mg	• First line therapy for productive / wet cough • Tablet is most concentrated dosage form • Adequate fluid intake is required for efficacy	Y/N*
Saline Nebs	Initial: 3ml inhalation q4h	Saline bullets: 3ml 0.9% vial	• Systemic absorption may lead to water retention	-
ANTITUSSIVE / COUGH SUPPRESSANT PLUS EXPECTORANT COMBINATIONS				
Guaifenesin/Codeine (Robitussin AC)	Initial: 5-10ml PO q4h PRN MDD: 60ml/day	Syrup: 10mg codeine/ 100mg guaifenesin in 5ml	• Adequate fluid intake is required for efficacy • Consider if unbearable symptoms due to productive cough; cough suppressant component may limit clearing of thick pulmonary mucus	-
Guaifenesin/ Dextromethorphan (Robitussin DM, Mucinex DM, Mucinex DM Max)	Initial (solution): 5-10 ml PO q4h PRN Initial (ER tablet): 1-2 PO BID of 30/600mg or 1 PO BID of 60/1,200mg tablets MDD (solution): 60 ml MDD (ER tablet): 120mg DM / 2,400mg guaifenesin	Syrup: 10mg dextromethorphan./ 100mg guaifenesin in 5ml Tablet (ER): 30mg dextromethorphan / 600mg guaifenesin, 60mg dextromethorphan/ 1,200mg guaifenesin	• Adequate fluid intake is required for efficacy • Consider if unbearable symptoms due to productive cough; cough suppressant component may limit clearing of thick pulmonary mucus	N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTITUSSIVE / COUGH SUPPRESSANT PLUS ANTIHISTAMINE COMBINATIONS				
Hydrocodone/ Chlorpheniramine (Tussionex, Tussicaps, Vituz)	Initial (ER suspension): 5ml PO BID Initial (solution): 5ml Q4-6 hours PRN; NTE 4 doses/day Initial (ER capsule): 1 capsule PO Q12 hours MDD (ER suspension): 10ml/day MDD (solution): 20ml/day MDD (ER capsule): 2 capsules/day	Capsule (ER): 5mg hydrocodone/4mg chlorpheniramine, 10mg hydrocodone/8mg chlorpheniramine Solution: 5mg hydrocodone/4mg chlorpheniramine / 5ml Suspension (ER): hydrocodone bitartrate 10mg and chlorpheniramine maleate 8mg per 5ml	• CII controlled substance • Initial doses are equivalent to max daily doses; do not titrate • Expensive	N
Promethazine/ Codeine (Phenergan AC)	Initial: 5ml PO q4-6h PRN MDD: 30ml/day	Syrup: codeine 10mg and promethazine 6.25mg in 5ml	• Avoid in patients with Parkinson disease due to potential for causing EPS • Abuse potential increasing in U.S.	-
Promethazine/ Dextromethorphan (Phenergan DM)	Initial: 5ml PO q4-6h PRN MDD: 30ml/day	Syrup: dextromethorphan 15mg and promethazine 6.25mg in 5ml	• Avoid in patients with Parkinson disease due to potential for causing EPS	-
LOCAL ANESTHETICS				
Bupivacaine (Marcaine)	Initial: 5ml of 0.25% solution nebulized TID-QID PRN MDD: not established for this indication	Solution for injection: 0.25%, 0.5%, 0.75%	• For refractory cough • No oral intake for 1-2 hours after admin to minimize aspiration risk • Duration of action varies widely from as little as 10 minutes up to prolonged relief for as long several weeks	-
Lidocaine (Xylocaine)	Initial: 5ml of 2% solution nebulized TID-QID PRN MDD: Not established for this indication	Solution for injection: 1% (10mg/ml),2%(20mg/ml), 4% (40mg/ml)	• For refractory cough • No oral intake for 1-2 hours after admin to minimize aspiration risk • Duration of action varies widely from as little as 10 minutes up to prolonged relief for as long several weeks	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
GABAPENTINOIDS				
Gabapentin (Neurontin)	Initial: 300mg PO QHS Titrate dose gradually in 300mg increments MDD: 1,800mg/day	Capsule: 100mg, 300mg, 400mg Oral solution: 250mg/5ml Tablet: 600mg, 800mg	**Gabapentinoids** • May be effective for refractory idiopathic cough • Require renal dose adjustments • May cause dizziness, drowsiness, dry mouth, headache, sedation • May cause peripheral edema; use caution in patients with heart failure **Gabapentin** • Case reports of rapid symptom relief in patients with cancer	Y
Pregabalin (Lyrica)	Initial: 75mg PO QD Titrate gradually over first week in increments of 75mg/day MDD: 300mg/day	Capsule: 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg Oral Solution: 20mg/ml		Y

References

- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 663-7.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 218-223.
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 80.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 229,1117,1131-1133,1237-1239.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 196-197.
- Silvestri, R. et al. Evaluation of subacute and chronic cough in adults, UpToDate, literature review current through Nov. 2015.
- von Gunten, C. et al. Palliative care: Overview of cough, stridor, and hemoptysis, UpToDate, literature review current through Nov. 2015.

Delirium

DEFINITION

Delirium is an acute change in mental status associated with medical illness that may fluctuate and can manifest clinically with a wide range of neuropsychiatric abnormalities.

CAUSES

- Any terminal illness
- Physiological
  - Constipation
  - Urinary retention
  - Electrolyte imbalance (sodium and calcium in particular)
  - Low albumin
  - Hyperparathyroidism
  - Glucose changes (hyper or hypoglycemia)
  - Vitamin deficiencies (vitamins B1, B12, niacin, folic acid in particular)
  - Acid-base disorders
  - Heavy metal toxicities
  - Dehydration
  - Hypoxia
  - Hypotension
  - Hypertensive encephalopathy
  - Shock
  - Head trauma
  - Hemorrhage
  - Seizure
- Infection
  - Urinary tract
  - Pneumonia
  - Sepsis
  - Encephalitis
  - Meningitis
  - HIV
  - Syphilis
- Medication use (especially opioids, corticosteroids, benzodiazepines, anticholinergics)
- Medication/substance withdrawal/discontinuation (alcohol, barbiturates and sedative hypnotics in particular)
- Other risk factors
  - Depression
  - Previous delirium
  - Fractures

HOW TO RECOGNIZE SYMPTOM

- Delirium is associated with the acute onset of symptoms over hours to days (onset may have occurred in the past). Signs and symptoms, which may be persistent or fluctuate include:
  - Altered level of consciousness such as hypervigilance, alertness, lethargy, cloudiness, stupor
  - Agitation that may be verbal/physical, aggressive/non-aggressive
  - Behavioral disinhibition
  - Disorganized thoughts
  - Disorientation to person, place, time or situation
    - It has been suggested that the most useful screening question for assessing altered mental states may be “what time of day is it?”
  - Inattention / impaired concentration
  - Irritability
  - Psychosis, including hallucinations or delusions
  - Rapidly changing affect or mood
  - Restlessness
  - Sleep disturbance; insomnia and day-night reversal are common
- Hypoactive delirium typically progresses from: normal › sleepy › lethargic › obtunded › semicomatose › comatose › death
- Hyperactive delirium typically progresses from: normal › restless › confused › tremulous › hallucinations › mumbling › myoclonus › seizures › semicomatose › death

CLINICAL INSIGHTS

- Nearly all patients will experience delirium at some point during the dying process – usually they will experience a hypoactive type delirium.
- The presence of delirium may fluctuate
- Assessing each patient’s unique clinical situation is essential in guiding treatment – medical conditions, functional status, prognosis and goals of care must considered when determining the appropriate treatment approach.
- Goals of care change frequently as terminal illnesses evolve and decision makers will often reassess goals of care after a delirium diagnosis.

- Non-pharmacological interventions, including family/ caregiver support should be included in every delirium management plan.
- Pain does not cause delirium, although uncontrolled pain can worsen delirium symptoms

TABLE 1 – NON-PHARMACOLOGICAL INTERVENTIONS FOR DELIRIUM

TYPE OF INTERVENTION	COMMENTS
Minimize medications	Review medication profile with intent to discontinue unnecessary medications
Environmental	Provide familiar surroundings that avoids overstimulation as well as sensory deprivation Allow uninterrupted sleep and promote a normal sleep-wake cycle
Behavioral	Look patient in the eye when communicating Provide clear and simple instructions Avoid confrontation (of delusional beliefs)
Sensory	Use eyeglasses or hearing aids as possible
Restraints	Avoid whenever possible (including urinary catheters, oxygen tubing, IV lines)

- Delirium can be divided into six subtypes by whether the delirium is potentially reversible or irreversible and whether it presents as hypoactive, hyperactive or a mix of both. Drug treatment strategies differ based on subtype (**Table 2**).

TABLE 2 – DELIRIUM SUBTYPES AND SUGGESTED TREATMENT STRATEGIES

	HYPERACTIVE	MIXED	HYPOACTIVE
Potentially reversible	Treatment strategy #1	Use clinical judgement	Treatment strategy #3
Irreversible	Treatment strategy #2	Use clinical judgement	Treatment strategy #3

- There is a lack of consensus regarding delirium management across different specialties of medicine
- No medications are FDA approved for delirium but are used to, but evidence based strategies exist for successful delirium treatment using medications off-label
- All pharmacological strategies to manage delirium, regardless of type, can safely be administered in any setting, including patients' homes
- Medications used in delirium management can be rapidly titrated without compromising patient safety
  - » Until symptoms are controlled, medications should be dosed as frequently as possible, based on their time to maximum plasma concentrations (typically 60 minutes for oral, 30 minutes for SQ/ IM, 15minutes for IV)
  - » If the dose used initially requires titration, assess for adverse effects prior to giving the next dose
  - » Once symptoms are controlled, the total previous 24 hour amount of drug should be scheduled routinely, divided based on elimination half-life
- Dependent upon the patient's condition and plan of care, diagnostics that attempt to identify a potentially reversible cause and would lead to a specific treatment approach may be considered
  - » CBC
  - » BUN
  - » ABG
  - » Electrolytes
  - » Urinalysis
  - » Blood sugar
- Delirium may be considered irreversible if:
  - » The underlying causes are irreversible or attempts to determine causes have failed
  - » Diagnostics and/or attempts to reverse the delirium are not consistent with goals of care
  - » Attempts to reverse the delirium have failed
- Acute agitation crisis: during the management of delirium a patient may become so agitated that they represent an immediate danger to themselves or others
  - » Some advocate a SQ/IM cocktail of haloperidol (2-5mg), diphenhydramine (50-100mg) with or without lorazepam (1-2mg) to be injected every 30 minutes as needed until resolved

- To administer as a single injection these medications may be drawn up very slowly into the same syringe in the following order: lorazepam, haloperidol, diphenhydramine

TREATMENT STRATEGY #1 – POTENTIALLY REVERSIBLE HYPERACTIVE DELIRIUM

- First, attempt to remedy cause of reversible delirium when identifiable and consistent with goals of care
  - Ex: laxatives for constipation; IV bisphosphonates for hypercalcemia due to bone mets
- Benzodiazepines should not be used if the goal of therapy is to reverse delirium
  - Exceptions: alcohol withdrawal, acute agitation crisis
- First line therapy is with typical / 1st generation antipsychotics (ex: haloperidol)
  - To reduce agitation and other symptoms
  - Typical doses needed to manage symptoms are usually well below the drug's MDD
  - Atypical / 2nd generation antipsychotics may be considered, although there are fewer studies supporting their use, they have fewer routes of administration available, and are usually more expensive
  - The black box warning issued by the FDA regarding the increased risk of death with antipsychotic use in elderly demented patients did not consider data addressing short-term use to manage delirium and should not be extrapolated to delirium management of hospice patients

TREATMENT STRATEGY #2 – IRREVERSIBLE HYPERACTIVE DELIRIUM

- Treatment of this type of delirium is not equivalent to palliative sedation, although sedation may occur.
- This approach does not hasten death and may actually increase both quality and duration of life.
- Benzodiazepines are first line therapy, especially when signs and symptoms of the dying process are present (**Table 3**)
  - If a paradoxical reaction, such as behavioral disinhibition occurs with use, titration to higher doses will usually overcome the reaction and provide symptom control
- Antipsychotics represent alternate therapy and should be considered, especially if psychosis present
- Phenobarbital and/or propofol represent 2nd line therapies that should be considered if symptoms cannot be controlled with benzodiazepines and antipsychotics
- Benzodiazepines, antipsychotics, phenobarbital and propofol may be used in combination if needed to control symptoms

TABLE 3 – DISEASE SPECIFIC SIGNS OF THE DYING PROCESS

TERMINAL CONDITION	SIGNS OF THE DYING PROCESS
Cardiac disease	Tachycardia, decreased output/ volume, peripheral cooling, cyanosis, mottling, venous pooling
Renal failure	Progression to anuria
Pulmonary disease	Tachypnea, abnormal breathing patterns
Neurological	Loss of eyelash/gag reflexes, swallowing ability, sphincter control, seizures

TREATMENT STRATEGY #3 – HYPOACTIVE DELIRIUM

- Little evidence exists to guide treatment and there is no clear consensus approach; some advocate to avoid pharmacological intervention
- When psychosis is present, targeted use of antipsychotics can be considered and would be dosed similarly to treatment strategies 1 & 2
- No evidence exists to guide the use of benzodiazepines

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MEDICATIONS USED IN TREATMENT STRATEGY #1 – POTENTIALLY REVERSIBLE HYPERACTIVE DELIRIUM				
Chlorpromazine (Thorazine)	Initial (PO/PR): 25-50mg Q hour PRN Initial (IM): 25-50mg Q30min. PRN Initial (IV): 25-50mg Q15min. PRN MDD: 2,000mg/day	Solution for injection: 25mg/ml Tablet: 10mg, 25mg, 50mg, 100mg, 200mg	• Once acute symptoms are controlled, schedule previous 24 hour amount used divided QD-BID and continue to use the last previous effective PRN • Useful if sedation is desired • Potential to cause orthostatic hypotension • PO:INJ is 4:1 • MDD rarely exceeded in this setting • Injection is expensive	Y
Haloperidol (Haldol)	Initial (PO/PR): 1-2mg Q hour PRN Initial (SQ/IM): 1-2mg Q30min. PRN Initial (IV): 1-2mg Q15min. PRN MDD: 100mg/day	Oral solution: 2mg/ml Solution for injection (lactate): 5mg/ml Tablet: 0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg	• Once acute symptoms are controlled, schedule previous 24 hour amount used divided QD-BID and continue to use the last previous effective PRN • Most commonly used/studied medication for delirium • Although not indicated, haloperidol lactate injection is commonly administered by SQ route in the hospice setting • Tablet and oral solution have demonstrated PR / SL uses • PO:INJ is 2:1 • MDD rarely exceeded in this setting • Injection is expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MEDICATIONS USED FOR TREATMENT STRATEGY #2 – IRREVERSIBLE HYPERACTIVE DELIRIUM				
Chlorpromazine (Thorazine) Haloperidol (Haldol)	Same as treatment strategy #1			
Lorazepam (Ativan)	Initial (PO/PR): 1-2mg Qhour PRN Initial (SQ/IM): 1-2mg Q30min. PRN Initial (IV): 1-2mg Q15min. PRN MDD: 40mg/day	Oral solution: 2mg/ml Solution for injection: 2mg/ml Tablet: 0.5mg, 1mg, 2mg	• Once acute symptoms are controlled, schedule previous 24 hour amount used divided BID and continue to use the last previous effective PRN • Avoid rectal route due to unreliable and delayed absorption	Y
Midazolam (Versed)	Initial (SQ/IM): 0.1-0.2mg/kg Q30min. PRN Initial (IV): 0.1-0.2mg/kg Q15min. PRN MDD: 240mg/day	Solution for injection: 1mg/ml, 5mg/ml	• Once acute symptoms are controlled, give 25% of the total dose needed to control symptoms per hour as a continuous infusion and give 0.1mg/kg doses PRN (Q30min. if SQ/IM; Q15min. if IV) • Patients respond to a wide range of doses. Doses must be individualized	-
Phenobarbital (Luminal)	Initial (PO/PR) 30-120mg/day divided BID-TID PRN Initial (SQ/IV): 10-30mg/kg loading dose,then20-100mg/hr continuous infusion MDD: 2,400mg/day	Elixir: 20mg/5ml Oral solution: 20mg/5ml Solution for injection: 65mg/ml, 130mg/ml Tablet: 7.5mg, 15mg, 16.2mg, 30mg, 32.4mg, 60mg, 64.8mg, 97.2mg, 100mg	• Reserve infusion for severely agitated patients with doses needed that exceed max volume per SQ/IM bolus	Y
Propofol (Diprivan)	Initial: 1mg/kg/hr continuous IV infusion	Emulsion for injection: 10mg/ml	• Titrate by 0.5mg/kg every 30min. until symptom control • Usual effective dose is < 6mg/kg/hr • Last line therapy • Requires specialized tubes and training for safe administration	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MEDICATIONS USED FOR TREATMENT STRATEGY #3 – HYPOACTIVE DELIRIUM				
Chlorpromazine (Thorazine)	Same as treatment strategy #1			
Haloperidol (Haldol)				

References

- Bruera, E. et al. Overview of managing common non-pain symptoms in palliative care, UpToDate, literature review current through Nov. 2015.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 688-700.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 190-199.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3g: delirium, accessed online Nov. 2015 at: http://www.cancer.gov/resources-for/hp/education/epeco/self-study/module-3/module-3g.pdf
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 72.
- Francis Jr., J. et al. Delirium and acute confusional states: Prevention, treatment and prognosis, UpToDate, literature review current through Nov. 2015.
- Francis Jr., J. et al. Diagnosis of delirium and confusional states, UpToDate, literature review current through Nov. 2015.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 422, 689,1042-4,1066,1467-1475,1556.
- Irwin, S. et al. Clarifying delirium management: practical, evidenced-based, expert recommendations for clinical practice, Journal of Palliative Medicine, 2013, Vol. 16, No.4.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 245.

Depression
(Major Depression)

DEFINITION

A serious medical condition in which a person feels very sad, hopeless, unimportant and is often unable to live in a normal way.

CAUSES

- Thought to be due to the chronic activation of the HPA, which regulates substances in the body that can increase depressive or other sickness-related symptoms. Imbalance of hormones in the brain may further precipitate this dysfunction.
- Organic events such as the direct effects of a medical illness
- Vitamin deficiencies, electrolyte disturbances and neurological conditions such as seizures, dementia or delirium
- Medication side effects
  - » baclofen, benzodiazepines, beta-blockers, corticosteroids, diuretics, opioids
- Premature or abrupt discontinuation of antidepressants
- Depressive disorders (major depressive disorder, dysthymia)
- Any terminal illness
- Social or spiritual issues
- Unrelieved pain

HOW TO RECOGNIZE SYMPTOM

- Patient exhibits five (or more) of the following symptoms for at least 2 weeks (one symptom is either depressed mood or loss of interest/pleasure):
  - » Depressed mood most of the day, or nearly every day
  - » Loss if interest or pleasure in activities
  - » Significant weight loss or weight gain or increase or decrease in appetite
  - » Insomnia or hypersomnia
  - » Psychomotor agitation or retardation
  - » Fatigue
  - » Feelings of worthlessness or guilt
  - » Difficulty concentrating
  - » Recurrent thoughts of death or suicide
- Because many of the symptoms of depression overlap with symptoms commonly experienced by hospice patients, it has been suggested that diagnosis should focus on a patient-specific assessments of feelings of helplessness, worthlessness and inappropriate guilt.
- The gold standard for diagnosis is a specialized diagnostic interview, however, since this is unlikely to be completed in the hospice setting other methods to diagnose should be considered

CLINICAL INSIGHTS

- The prevalence of depression at the end of life has been estimated at about 25%
- Although depression is common, it is easily overlooked and is likely undertreated in the hospice setting
- The one-item depression screening question "Are you depressed?" has been shown to reliably predict a diagnosis of depression with high specificity and sensitivity
- Depression is strongly and consistently associated with a poor quality of life
- Inadequate dose titration is a common reason for treatment failure of depression in elderly patients; plan to titrate to usual effective doses if tolerated
- Do not assume that depression is a normal part of the dying process; it is different than preparatory grief (**Table 1**)

TABLE 1 – DIFFERENTIATING PREPARATORY GRIEF VS. DEPRESSION

CHARACTERISTIC	PREPARATORY GRIEF	DEPRESSION
Temporal variation	Experienced in waves	Persistent
Progress with time	Improves over time	Does not improve over time
Self-image	Normal for individual	Sense of worthlessness
Pleasure	Ability still present	Absent or diminished
Hope	Maintains	Pervasive loss
Response to support	Social interaction helps	No pleasure from social interaction
Active desire for early death	Possible, but diminishes with time	Persistent and active desire

- All antidepressants are approximately equal in their ability to improve symptoms of depression (exceptions include trazodone and bupropion)
- It may take several drug trials to find an effective treatment for depression

- Choice of antidepressant should be dictated by the following:
  - » Previous success or treatment failure to a particular antidepressant by the patient or a 1st degree relative
  - » Pharmacokinetic profile (half-life, drug-drug interactions, side-effect profile) (**Table 2**)

TABLE 2 – COMPARISON OF COMMONLY USED SSRIS

	SSRI				
	Celexa (citalopram)	Lexapro (escitalopram)	Zoloft (sertraline)	Prozac (fluoxetine)	Paxil
Drug Interactions	fewest	fewest		strong CYP2D6 inhibitor	strong CYP2D6 inhibitor
Adverse Effects	QT-interval prolongation		most G.I. related (esp. diarrhea) of SSRIs	most short-term weight loss and activation	most sedating and anticholinergic SSRI; most nausea; most weight gain
Half-life				longest; allows for natural taper	shortest; more likely discontinuation rxn
Price		more than other generic SSRIs			

- » Prognosis
  - ° Many of the traditional medications for depression, such as SSRI's may take 4 to 6 weeks to reach full effect
  - ° Psychostimulants and possibly ketamine offer an immediate onsets of action and therefore may be preferred for the treatment of depression in patients with a prognosis measured in weeks or less
- » Comorbidities
  - ° Examples: bupropion is contraindicated if patient has a seizure disorder; duloxetine is contraindicated if patient has severe liver disease
- » Other symptoms – antidepressants with multisymptom benefit should be considered preferentially; this reduces pill burden, chance of drug interactions, adverse effects, and hospice drug spend
  - ° Characteristics and side effects can potentially be used to therapeutic advantage to manage multi-symptom clusters, for example:
  - ° Anorexia – Mirtazapine
  - ° Insomnia – trazodone, TCAs, low dose Mirtazapine
  - ° Neuropathic pain – TCAs, SNRIs
  - ° Anxiety – SSRIs, SNRIs, TCAs, Mirtazapine

- Monoamine oxidase inhibitors (MAOIs) are not recommended in hospice care
- St. John's wort is an over the counter supplement that patients may take for depression; its use cannot be recommended due to uncertainty about appropriate doses, variation among preparations and unknown potential for serious drug-drug interactions.
- TCAs, especially amitriptyline, commonly cause anticholinergic adverse effects, including: confusion, psychosis, delirium, tachycardia and constipation; avoid in elderly patients, demented patients and patients with severe cardiac or renal disease.
- TCAs should be avoided in patients with suicidal ideation due to increased potential for fatality due to intentional overdose
- The likelihood of a patient receiving multiple different antidepressants and other serotonergic agents (**Table 3**) is increased in the hospice setting due to off-label use (ex: trazodone for insomnia). If use of multiple antidepressants and/or serotonergic agents cannot be avoided, monitor for signs and symptoms of serotonin syndrome (diaphoresis, tachycardia, hyperthermia, hypertension, hyperreflexia, clonus/ myoclonus)

TABLE 3 – NON-ANTIDEPRESSANT MEDICATIONS WITH CLINICALLY RELEVANT SEROTONERGIC POTENCY

MEDICATION CLASS	
Psychostimulants	Dextroamphetamine, but not methylphenidate
H1 Antihistamines	Only chlorpheniramine, brompheniramine
Opioids / Opioid Like	Only dextromethorphan, propoxyphene, fentanyl, methadone, pentazocine, meperidine, tramadol; but not other opioids
Miscellaneous Agents with Mao Activity	Furazolidone, linezolid, methylene blue, procarbazine, selegiline (antiparkinsonian)

- Single doses of oral ketamine (dosed at 0.5mg/kg one time) has been successfully attempted in multiple case studies for immediate and lasting reversal of depression
- Initial response time to antidepressants may be augmented by a temporary overlap with psychostimulants or benzodiazepines.
- Abruptly stopping an antidepressant after more than 8 weeks of therapy will commonly cause withdrawal symptoms that vary depending on the type of antidepressant stopped.
  - » SSRIs and SNRIs – "FINISH" flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal (restlessness, anxiety, agitation)
  - » TCAs – flu-like symptoms, insomnia, GI disorders, mood disorders, movement disorders (rare)
  - » Trazodone – flu-like symptoms, GI disorders, restlessness, tremor, headache
  - » Mirtazapine – nausea, dizziness, hyperarousal, headache

- Antidepressants may have negative effects on a number of other medical conditions or physiological processes, including:
  - » Reduced seizure threshold (dose dependent) –all types (bupropion contraindicated)
    - ° Risk is lowest with SSRIs, higher with TCAs and highest with bupropion
    - ° May be due to reduced seizure threshold, drug interactions or drug-induced hyponatremia
    - ° Except for bupropion, which is contraindicated, the clinical significance of this is not universally agreed upon; benefits may outweigh risk
  - » Extrapyramidal symptoms (EPS) – SSRIs
    - ° Due to serotonergic mediated inhibition of dopamine release
      - › The risk appears small and SSRIs may even be used preferentially in this setting, as other options, such as TCAs, can worsen autonomic dysfunction (ex: orthostasis) and cognition.
  - » Syndrome of inappropriate antidiuretic hormone hypersecretion – SSRIs, TCAs and SNRIs
    - ° Relatively rare, but probably underdiagnosed
    - ° Acute onset of confusion or mental status changes upon initiation of therapy should prompt investigation, potentially including BMP to check sodium level
      - › Discontinue treatment in patients with symptomatic hyponatremia
  - » Bleeding (particularly GI)– SSRIs, TCAs and SNRIs
    - ° Due to depletion of intraplatelet serotonin stores, which are needed for platelet aggregation
    - ° Risk increased with concomitant NSAID use

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)				
Citalopram (Celexa)	Initial: 10-20mg PO daily MDD: 40/day (20mg if > 60yo or significant liver or cardiac disease)	Oral solution: 10mg/5ml Tablet: 10mg, 20mg, 40mg	• Less drug interactions than other SSRIs • More cost effective than escitalopram	Y
Escitalopram (Lexapro)	Initial: 5-10mg PO daily MDD: 20mg/day	Oral solution: 5mg/5ml Tablet: 5mg, 10mg, 20mg	• Less drug interactions than other SSRIs • Active enantiomer of citalopram • Use caution if CrCl < 30ml/min • More expensive than other generic SSRIs	Y
Fluoxetine (Prozac, Prozac Weekly)	Initial: 10-20mg PO daily MDD: 80mg/day	Capsule: 10mg, 20mg, 40mg Capsule (DR, weekly)*: 90mg Oral solution: 20mg/5ml	• More drug interactions than other SSRIs • Long half-life allows for natural taper if abruptly discontinued, avoiding withdrawal symptoms	Y/N*
Paroxetine (Paxil, Paxil CR)	Initial: 10mg PO daily (CR: 25mg PO daily) MDD: 50mg/day (CR: 62.5mg/day)	Oral suspension: 10mg/5ml Tablet: 10mg, 20mg, 30mg, 40mg Tablet (CR)*: 12.5mg, 25mg, 37.5mg	• More drug interactions than other SSRIs • Most sedating and anticholinergic SSRI • Use caution if CrCl < 30ml/min or significant liver disease	Y/N*
Sertraline (Zoloft)	Initial: 25-50mg PO daily MDD: 200mg/day	Oral solution: 20mg/ml Tablet: 25mg, 50mg, 100mg	• Less drug interactions than other SSRIs • More GI-related adverse effects than other SSRIs • Use caution / reduced doses if significant liver disease • Most concentrated oral solution; potentially useful if patient has severe dysphagia	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
TRICYCLIC ANTIDEPRESSANTS (TCAS)				
Amitriptyline (Elavil)	Initial: 25-50mg PO QHS MDD: 300mg/day	Tablet: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	• Consider if comorbid insomnia or neuropathic pain • Most anticholinergic TCA	Y
Desipramine (Norpramin)	Initial: 25-50mg PO QHS MDD: 300mg/day (150mg/day if elderly)	Tablet: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	• Consider if comorbid insomnia or neuropathic pain • Least anticholinergic TCA (equal to nortriptyline)	Y
Doxepin (Sinequan)	Initial: 25-50mg PO QHS MDD: 300mg/day	Capsule: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg Oral solution: 10mg/ml Tablet: 3mg, 6mg	• Consider if comorbid insomnia, neuropathic pain or pruritus • Consider if patient is experiencing depression as a result of alcohol withdrawal • If using oral solution dilute dose in at least 4 ounces of a non-carbonated beverage just prior to administration	Y
Nortriptyline (Pamelor)	Initial: 25-50mg PO QHS MDD: 150mg/day	Capsule: 10mg, 25mg, 50mg, 75mg Oral solution: 10mg/5ml	• Consider if comorbid insomnia or neuropathic pain • Least anticholinergic TCA (equal to desipramine)	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)				
Duloxetine (Cymbalta)	Initial: 40-60mg PO daily MDD: 120mg (doses more than 60mg per day not typically more effective, but associated with increased adverse effects)	Capsule: 20mg, 30mg, 60mg	• Consider if patient has comorbid neuropathic pain • Avoid if CrCl < 30ml/min • Contraindicated if liver impairment • Associated with increases in blood pressure, especially initially • Capsules may be opened and sprinkled onto apple sauce or into apple juice, but not chocolate pudding* • Expensive	Y*
Venlafaxine (Effexor XR)	Initial (IR): 37.5-75mg PO daily in 2-3 divided doses Initial (XR): 37.5-75mg PO QD MDD (IR): 375mg/day MDD (XR): 225mg/day	Capsule (XR)*: 37.5mg, 75mg, 150mg Tablet: 25mg, 37.5mg, 50mg, 75mg, 100mg Tablet (XR)*: 37.5mg, 75mg, 150mg, 225mg	• Associated with dose-dependent increases in blood pressure • Administer extended release forms as a single daily dose at approximately the same time every day • Do not crush or chew • XR capsules can be sprinkled on apple sauce and swallowed, immediately followed by a glass of water to ensure ingestion • Consider if comorbid neuropathic pain • Dose adjustment required if renal impairment	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MISCELLANEOUS SEROTONIN / ALPHA RECEPTOR ANTAGONISTS				
Mirtazapine (Remeron, Remeron SolTab)	Initial: 7.5-15mg PO daily MDD: 45mg/day	Oral Disintegrating Tablet (ODT): 15mg, 30mg, 45mg Tablet: 7.5mg, 15mg, 30mg, 45mg	• Potential multisymptom benefit, including: anorexia, insomnia, anxiety, certain types of itching • More sedating at lower doses (7.5-15mg/day) • More rapid onset than other antidepressants (potentially as soon as 1 week vs. multiple weeks for others)	Y
Trazodone (Desyrel)	Initial: 50mg PO bedtime MDD: 600mg/day	Tablet: 50mg, 100mg, 150mg, 300mg Tablet (ER): 150mg, 300mg	• Sedating • Less effective than other types of antidepressants • Consider as adjunct therapy for antidepressant induced insomnia	Y
NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIBITOR (NDRI)				
Bupropion HCl (Wellbutrin, Wellbutrin SR, Wellbutrin XL)	Initial: IR 100mg BID; increase after 3 days SR 150mg QAM; increase after 3 days XL 150mg QAM; increase after 4 days MDD (IR): 450mg/day MDD (SR): 400mg/day MDD (XL): 300mg/day	Tablet: 75mg, 100mg Tablet (SR, 12 hour)*: 100mg, 150mg, 200mg Tablet (XL, 24 hour)*: 150mg, 300mg	• Contraindicated in patients with seizure disorder • ER forms should be swallowed whole and not crushed or chewed • Less effective than other types of antidepressants	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
PSYCHOSTIMULANTS				
Dextroamphetamine (Dexedrine)	Initial: 2.5-5mg PO QAM MDD: 20mg/day	Tablet: 5mg, 10mg	• Off label use • Rapid onset as quickly as within one day is of great advantage in the hospice setting • Use only immediate release dosage forms for depression • Give in the morning and at noon or not later than 2pm to prevent insomnia • Can be used alone or in combination with SSRI or TCA to augment antidepressant onset • Use with caution in patients with cardiac disease or uncontrolled hypertension • More expensive than methylphenidate	Y
Methylphenidate (Methylin, Ritalin)	Initial: 2.5-5mg PO BID MDD: 20-40mg/day	Chewable tablet: 2.5mg, 5mg, 10mg Oral solution: 5mg/5ml, 10mg/5ml Tablet: 5mg, 10mg, 20mg	• Off label use • Rapid onset as quickly as within one day is of great advantage in the hospice setting • Use only immediate release dosage forms for depression • Give in the morning and at noon or not later than 2pm to prevent insomnia • Can be used alone or in combination with SSRI or TCA to augment antidepressant onset • Use with caution in patients with cardiac disease or uncontrolled hypertension • Lacks serotonergic activity; does not increase risk of serotonin syndrome	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DISSOCIATIVES				
Ketamine (Ketalar)	Initial: 0.5mg/kg x 1 dose rounded to nearest 5mg increment. May repeat dose as needed if effects wear off. May titrate to once daily dosing if needed. MDD: not established for this indication, although highest dose studied is 0.5mg/kg TID.	Solution for injection: 10mg/ml, 50mg/ml, 100mg/ml	• Disassociative anesthetic used off-label at subanesthetic doses for antidepressant effect • The injectable form may be taken orally, or an oral solution may be compounded to improve taste and tolerability • Very effective (approximately 70% response), even in patients with treatment-resistant depression. • Consider in patients with suicidal ideation • Can be used for both Major Depressive Disorder (MDD) and bipolar depression • Improves depressive symptoms much more rapidly than conventional antidepressants (patients often respond within hours) • Beneficial effects are typically transient and persist for about 1 week on average • May cause both psychiatric (eg, euphoria, psychosis, delirium) and somatic (eg, hypertension, tachycardia, hypersalivation, raised intracranial pressure, GI distress, and cystitis) side effects, although subanesthetic doses used for depression are typically well-tolerated • In some cases, adverse effects can be mitigated with other medications (ex: haloperidol for delirium, labetalol for HTN/tachycardia) • Avoid in patients with schizophrenia (and similar disorders), those with raised intracranial pressure and those with conditions where increased BP/ HR would be hazardous • Antidepressant mechanisms of action may be distinct from NMDA receptor antagonism. Hepatic metabolism to active metabolites is thought to be required, therefore its effect may be reduced or absent in cirrhotic patients	-

References

- Ieksandrova, L. Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism, J Psych Neurosci, 2017.
- Ali, R. et al. Letter to the Editor, American Journal of Hospice and Palliative Medicine, Vol 23, No. 4, 2006.
- Block, S. et al. Assessing and Managing Depression in the Terminally Ill Patient, Annals of Internal Medicine, 2000;132:209-218.
- Boschert, S. Antidepressants Safe in End-Stage Liver Disease, Clinical Psychiatry News, April 2006.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 675-87.
- Burrows, G. et al. Mirtazapine – Clinical Advantages in the Treatment of Depression, Journal of Clinical Psychopharmacology, 1997: Vol 1, pp. 34-39.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 325-332.
- Ciechanowski, P. Unipolar major depression in adults: Choosing initial treatment, UpToDate, current through Aug 2015, accessed online 9/15/15.
- Ciraulo, D. et al. Clinical Pharmacology and Therapeutics of Antidepressants, Pharmacotherapy of Depression, 2011, pp. 33-124.
- Consumer reports best buy drugs – Using antidepressants to treat depression, 2013. Accessed online 9/15/15 at: https://www.consumerreports.org/health/resources/pdf/best-buy-drugs/Antidepressants_update.pdf
- Dibello, K. Grief & Depression at the end of life, The Nurse Practitioner, Vol. 40, No. 5, May 2015.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3h: Depression, accessed online Nov. 2015 at: http://www.ipcrc.net/epco/EPEC-O%20M03a-q%20Symptoms/EPEC-O%20M03h%20Depression/EPEC-O%20M03h%20Depression%20PH.pdf
- Esposito, P. et al. The Syndrome of Inappropriate Antidiuresis: Pathophysiology, Clinical Management and New Therapeutic Options, Nephron Clinical Practice, 2001; 119:c62-c73.
- Fan, W. et al. Ketamine rapidly relieves acute suicidal ideation in cancer patients: a randomized controlled clinical trial, Oncotarget, 2017;8(2):2356-60.
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 82.
- Garrison, C. et al. Predictors of Quality of Life in Elderly Hospice Patients With Cancer, Journal of Hospice and Palliative Nursing, Vol 13, No. 5, September/October 2011.
- Gould, et al. Ketamine mechanism of action: Separating the wheat from the chaff, Neuropsychopharmacology Reviews, (2017)42:368-9.
- Handsaker, S. et al. Identifying and treating depression at the end of life and among the bereaved, International Journal of Palliative Nursing, 2012 Vol 18, No. 2.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 1457-1463.
- Hannon, B. et al. Treatment of depression as part of end-of-life care, BMJ Case Reports, 2008, Nov. 20
- Hirsh, M. et al. Selective serotonin reuptake inhibitors: Pharmacology, administration and side effects, UpToDate, literature review current through August 2015; accessed online 9/18/15.
- Hotopf, M. et al. Depression in advanced disease: a systematic review Part 1. Prevalence and case finding, Palliative Medicine, 2002; 16: 81-97.
- Howard, P. et al. Therapeutic Reviews: Antidepressant Drugs, Journal of Pain and Symptom Management, Vol. 4, No. 5, 2012.
- Iglewicz, A. et al. Ketamine for the treatment of depression in patients receiving hospice care: a retrospective medical record review of thirty-one cases, Psychosomatics, 2015;56(4):329-337.
- Irwin, S. et al. Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial, J of Pall Med, 2013;16(8):958.
- Irwin, S. et al. Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care, J of Pall Med, 2010;13(7):903.
- Irwin, S. et al. Psychiatric Issues in Palliative Care: Recognition of Depression in Patients Enrolled in Hospice Care, Journal of Palliative Medicine, Vol. 11, No. 2, 2008.
- Irwin, S. et al. The Opportunity for Psychiatry in Palliative Care, The Canadian Journal of Psychiatry, Vol 53, No 11, Nov. 2008.
- Jacob, S. et al. Hyponatremia Associated with Selective Serotonin-Reuptake Inhibitors in Older Adults, The Annals of Pharmacotherapy, 2006 Vol 40, pp 1618-1622.
- Jin Ko, H. et al. The Association between Pain and Depression, Anxiety, and Cognitive Function among Advanced Cancer Patients in the Hospice Ward, Korean Journal of Family Medicine, 2013;34:347-356.
- Katz, M. Onset of clinical action of antidepressants, INHN, accessed online: http://inhn.org/controversies/martin-m-katz-onset-of-clinical-action-of-antidepressants.html
- Kimmel, P. Depression in end-stage renal disease patients: a critical review, Advances in Chronic Kidney Disease, 2007 Oct; 14(4):328-34.
- Lavretsky, H. et al. Combined Treatment With Methylphenidate and Citalopram for Accelerated Response in the Elderly: An Open Trial, Journal of Clinical Psychiatry, 64:12, December 2003.
- Lawrie, I. et al. How do palliative medicine physicians assess and manage depression, Palliative Medicine 2004; 18: 234-238.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Lloyd-Williams, M. et al. A survey of antidepressant prescribing in the terminally ill, Palliative Medicine, 13:243-248, 1999.
- Lloyd-Williams, M. Is it appropriate to screen palliative care patients for depression? American Journal of Hospice & Palliative Care, Vol. 19, No. 2, March/April 2002.
- Lowry, F. Late-life depression can be slow to respond to treatment, Medscape article accessed online 9/7/15 http://www.medscape.com/viewarticle/850588?src=emailthis
- Machado-Vieira, R. et al. The Timing of Antidepressant Effects: A Comparison of Diverse Pharmacological and Somatic Treatments, Pharmaceuticals, 2010 (3) 19-41.
- Marken, P. et al. Selecting a Selective Serotonin Reuptake Inhibitor: Clinically Important Distinguishing Features, Journal of Clinical Psychiatry, 2:6, December 2000.
- Miller, K. et al. Antidepressant medication use in palliative care, American Journal of Hospice & Palliative Medicine, Vol. 23, No. 2, March/April 2006.
- Orr, K. et al. Psychostimulants in the Treatment of Depression – A Review of the Evidence, CNS Drugs, 2007; 21(3):239-257.
- Panagioti, M. Overview of the prevalence, impact and management of depression and anxiety in chronic obstructive pulmonary disease, International Journal of COPD, 2014:9 1289-1306.
- Paolucci, S. Epidemiology and treatment of post-stroke depression, Neuropsychiatric Dis. Treat. 2008 Feb; 4(1): 145-154.
- Quibell, R. et al. Therapeutic Reviews: Ketamine, Journal of Pain and Symptom Mgmt, 2015;50(2):268-78.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 253.
- Reijnders, J. et al. A systematic review of prevalence studies of depression in Parkinson's disease, Movement Disorders, 2008 Jan 30;23(2): 183-9; quiz 313.
- Shiroma, P. Antidepressant Prescription Patter in a Hospice Program, American Journal of Hospice and Palliative Medicine, 28(3) 193-197, 2011.
- Shuster, J. Can Depression Be a Terminal Illness? Journal of Palliative Medicine, Vol 3. No. 4, 2000.
- Unipac 9, The Hospice and Palliative Medicine Approach to Selected Chronic Illnesses: Dementia, COPD and CHF, p. 22.
- Warden, D. et al. The STAR*D Project Results: A Comprehensive Review of Findings, Current Psychiatry Reports, 2007, 9:449-459.
- Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 873-893.
- Whipp, M. et al. Case report: Serotonin syndrome in the differential diagnosis of spinal cord compression, Palliative Medicine, 2004;18:69-70.
- Zanos, P. et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites, Nature, 2016;553:481-86.

Diarrhea

DEFINITION

Passage of frequent loose stools with urgency, often objectively defined as three or more unformed stools per 24 hours.

CAUSES

- Gastrointestinal disorders (most common causes of chronic diarrhea)
  - » Idiopathic
    - ° Irritable bowel syndrome (IBS)
  - » Inflammatory
    - ° Ulcerative colitis
    - ° Crohn's disease
    - ° Mucositis
    - ° Microscopic colitis
  - » Malabsorption syndromes
    - ° Short bowel syndrome
    - ° Celiac disease
    - ° Lactose intolerance
    - ° Cholecystectomy
    - ° Chronic pancreatitis
- Infection (most common cause of acute diarrhea)
  - » C. difficile
  - » Other viruses, bacterium or parasites
  - » Contaminated food / water
- Poor diet
- Medications and other substances
  - » Antibiotics
  - » Laxatives
  - » Magnesium containing antacids
  - » Chemotherapy
  - » Metformin
  - » Anti-retrovirals
  - » NSAIDs
  - » Colchicine
  - » Digoxin (chronic toxicity)
  - » Other substances such as alcohol, artificial sweeteners
- Malignancy
  - » Pancreatic cancer
  - » Colon cancer
  - » Carcinoid syndrome
  - » VIPoma
  - » Zollinger-Ellison syndrome
- Cancer-related treatments
  - » Radiation
  - » Bone marrow transplant
- Conditions that impair the passage of formed stools
  - » Partial bowel obstruction / fecal impaction
  - » Narcotized bowel
- Stress / anxiety / worry
- Graft-versus-host disease
- HIV/AIDs associated

HOW TO RECOGNIZE SYMPTOM

- Acute diarrhea – new onset of frequent, loose, watery stools with urgency
- Chronic diarrhea – presentations based on type (types are not mutually exclusive / may overlap)
  - » Inflammatory diarrhea
    - ° Crohn's disease
      - › Typically presents with diarrhea, abdominal pain, weight loss and fever
    - ° Ulcerative colitis
      - › Variable presentation depending on severity; rectal bleeding, blood stools, passage of mucus, cramping pain, anemia, fever and/or weight loss

- Watery
  - Functional types
    - Irritable bowel syndrome (IBS) – typically presents with cramping lower quadrant pain with diarrhea or constipation or alternating between the two; symptoms improve at night and with fasting
  - Secretory types (ex: microscopic colitis, carcinoid syndrome, Zollinger-Ellison syndrome, VIPoma)
    - Large volume (up to 2 liters per day), frequent watery diarrhea without bleeding; often persists despite fasting; more likely to occur at night than other types; varying frequency from a few to more than 30 per day
  - Osmotic types (ex: occurs with celiac disease, pancreatits or obstruction of bile duct)
- Malabsorption syndromes
  - Pale, greasy, voluminous, foul-smelling stools and weight loss despite adequate food intake

CLINICAL INSIGHTS

- Attempt to identify a potentially reversible cause prior to initiating treatment with pharmacotherapy
- Verify orders for routine laxatives are being held during periods of diarrhea
- Decision whether or not to treat and choice of medication should depend on type of diarrhea
  - Types of diarrhea based on duration:
    - Acute ≤ 14 days in duration
    - Persistent 14-29 days in duration
    - Chronic 30+ days in duration
- Acute diarrhea
  - Most cases are due to viral (more common) or bacterial (more severe) infections and are self-limiting
  - Dietary adjustments are first line therapy
    - "BRAT" diet is bananas, rice, apple sauce and toast
    - Avoid spicy foods and drinks and foods that are high in fat
    - Avoid fruit and fruitjuice
    - Oral rehydration products that are high in glucose and electrolytes to improve sodium and water absorption
  - Empiric antibiotic therapy should only be considered for severe, inflammatory diarrhea (hypovolemia, bloody stools, fever, ≥6 loose stools per day, duration > 1 week, severe abdominal pain, age ≥ 65 or immunocompromised)
  - It is reasonable to start metronidazole prior to confirming C. difficile associated diarrhea if characteristic foul smelling diarrhea is present, especially in the presence of known risk factors, such as recent antibiotic use, hospitalization or proximity to known C. difficile infection
  - Symptomatic therapy with motility slowing agents may be used in patients in whom fever is absent or low grade and without bloody stools
    - Use of antidiarrheal medications may delay symptom and infection resolution with C. difficile infection
- Chronic diarrhea
  - Treatment based on diagnosis
    - Chronic GI disorders – not discussed in this chapter
    - Secretory – octreotide is the drug of choice; cholestyramine may be beneficial
  - Symptomatic therapy with motility slowing agents is indicated when a definitive diagnosis is made, but treatment is unavailable, when a diagnosis cannot be determined and as temporary therapy prior to examination
- Careful perianal cleansing after episodes is essential to prevent complications such as infection and skin breakdown
- Although not indicated, all opioids may be beneficial due to their slowing of GI motility
- Watery diarrhea may be a sign of fecal impaction
- Foul smelling diarrhea may be a sign of infection

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MOTILITY SLOWING AGENTS				
Diphenoxylate/ Atropine (Lomotil)	Initial: 5mg QID then reduce the dose as needed MDD: 20mg/day	Oral solution: 2.5mg-0.025mg/5ml Tablet: 2.5mg/0.025mg	• 2nd line anti-motility agent • Controlled substance; a subtherapeutic amount of atropine is included to discourage abuse	Y
Loperamide (Imodium A-D)	Initial: 4mg PO once, then 2mg PO after each loose stool MDD: 16mg/day	Capsule: 2mg Oral solution: 1mg/5ml, 1mg/7.5ml Tablet: 2mg	• First line anti-motility agent • Available as OTC preparation • Contraindicated with colitis • Occasionally, exceeding the maximum daily dose may be warranted to control symptoms in the hospice setting	Y
Opium Tincture	Initial: 6mg PO QID MDD: 24mg/day	Tincture: 10mg/ml	• For refractory diarrhea • Opium tincture contains 25x more morphine than paregoric • Product contains 45% alcohol • Expensive	-
Paregoric	Initial: 5-10ml PO daily to QID MDD: 40ml/day	Tincture: 2mg/5ml	• Product contains 47% alcohol • Expensive	-
ANTIBIOTICS FOR TREATMENT OF C. DIFFICILE ASSOCIATED DIARRHEA				
Metronidazole (Flagyl)	Initial: 250-500mg PO/ IV TID to QID for 10-14 days MDD: 4,000mg/day	Capsule: 375mg Solution for injection: 500mg Tablet: 250mg, 500mg	• Do not consume alcohol or any alcohol containing products during therapy through 3 days after stopping to prevent severe symptoms due to disulfiram reaction • GI upset is the most common adverse effect	Y
Vancomycin (Vancocin)	Initial: 125mg PO QID for 10 days MDD: 2,000mg/day	Capsule: 125mg, 250mg Solution for injection: 500mg, 750mg, 1,000mg, 5,000mg	• Taken orally for this indication; medication is not absorbed and acts locally in the GI tract • Due cost, consider trial of metronidazole 1st; reserve use for severe symptoms or failure with metronidazole • Some experts recommend slowly tapering the dose and dosing frequency over the course of several weeks to ensure C. difficile spore eradication • Expensive; reconstituted powder for injection (not premixed solution) can be compounded into an oral solution to reduce cost	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTISECRETORY AGENTS				
Bismuth Subsalicylate (Pepto-bismol, Kaopectate)	Initial: 524mg PO every 30-60min. MDD: 4,200mg/day	Oral suspension: 262mg/15ml, 525mg/15ml, 527mg/30ml Tablet: 262mg	• Salicylate component is antisecretory and anti-inflammatory; bismuth component has antimicrobial activity • May cause black/tarry appearing stool	Y
Clonidine (Catapres, Kapvay)	Initial (PO): 0.1mg QD to TID Initial (transdermal): 0.1mg/24 hour patch changed once weekly MDD: 0.9mg/day	Tablet: 0.1mg, 0.2mg, 0.3mg Tablet (ER)*: 0.1mg Transdermal patch: 0.1mg/24 hours, 0.2mg/24 hours, 0.3mg/24 hours	• Not first line; consider when other options have failed • Has demonstrated efficacy in treating diarrhea of varying causes, such as IBS, infection, substance withdrawal, and malignancy • Exact mechanism of action not known, but thought to improve fluid and electrolyte absorption and inhibit secretions, leading to reduced stool volume and frequency and increased stool transit time. May also improve colonic and rectal tone, reducing stool urgency. • Average daily dose studied is 0.3mg/24 hours • Can cause hypotension	Y/N*
Octreotide (Sandostatin)	Initial: 50-100mcg IV/ SQ BID-TID MDD: 500mcg q 8 hours	Solution for injection: 50mcg/ml,100mcg/ml, 200mcg/ml,500mcg/ml, 1,000mcg/ml	• Particularly useful for diarrhea due to carcinoid tumors, Zollinger-Ellison syndrome, illeostomy and short-bowel syndrome • Expensive	-
BULK FORMING AGENTS				
Methylcellulose (Citrucel, others)	Initial: 1 tbsp (19 gm) or packet (10.7 gm) in 8oz cold water 1-3 times daily OR 2 tablets 6 X daily MDD: 1 tbsp TID OR 12 tablets/day	Powder: Bulk or 10.7gm packet Tablet: 500mg	• Must ensure adequate fluid intake for efficacy and to prevent bowel obstruction	Y
Polycarbophil calcium (Fibercon, others)	Initial: 2 tablets(1 gm) PO daily to QID MDD: 8 tablets/day	Tablet: 625mg	• Must ensure adequate fluid intake for efficacy and to prevent bowel obstruction	Y
Psyllium (Metamucil, others)	Initial: 2.5g PO daily to BID MDD: 30g/day	Capsule: 500mg Powder: 3.3gm/dose, 3.4gm/dose,6mg/dose Tablet: 4 tablets/dose Wafer: 1.7gm	• Must ensure adequate fluid intake for efficacy and to prevent bowel obstruction	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MISCELLANEOUS AGENTS				
Cholestyramine (Questran, Questran Light)	Initial: Use 1 packet (4gm) PO daily MDD: 24gm/day	Powder: 4gm packets for reconstitution (4g resin/5.7g powder, 4g resin/5g powder, 4g resin/9g powder)	• Particularly useful to treat diarrhea due to bile acid malabsorption • May be used as adjuvant therapy for C. difficile associated diarrhea – thought to work by binding and neutralizing toxin • May be beneficial with secretory diarrhea • Poorly tolerated due to frequent G.I. related adverse effects, including abdominal pain, bloating, fullness, nausea and flatulence • Reduces intestinal absorption of many different medications. Separating administration by 2 hours may reduce, but does not eliminate this risk.	-
Cyproheptadine (Periactin)	Initial: 4mg PO TID MDD: 48mg/day	Tablet: 4mg	• First line treatment for carcinoid syndrome • Antihistamine that is also used in the hospice setting to promote weight gain *(Continued on next page)*	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MISCELLANEOUS AGENTS (CONTINUED)				
Pancrelipase (Creon, Pancreaze, Pancrelipase, Pertzye, Ultresa, Viokace, Zenpep)	Initial: 500 units lipase/kg per meal MDD: 10,000 units lipase/kg/day	Capsule (DR, enteric coated pellets as units lipase)*: Creon: 3,000units, 6,000units, 12,000units, 24,000units, 36,000units Pancreaze: 4,200units, 10,500units, 16,800units, 21,000units Pertzye: 8,000units, 16,000units Ultresa: 13,800units, 20,700units, 23,000units Zenpep: 3,000units, 5,000units, 10,000units, 15,000units, 20,000units, 25,000units, 40,000units Tablet (Viokace): 10,440units, 20,880units	• Typically ½ the prescribed amount per meal is given with each snack • Viokace must be administered with a proton pump inhibitor since it is not enteric coated • Use caution in patients with renal impairment • *Capsules containing enteric coated pellets may be opened and sprinkled onto acid food, but contents should be swallowed whole and not crushed • Expensive	Y/N*

References

- Bruera, E. et al. Overview of managing common non-pain symptoms in palliative Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 560-6.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 244-247.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3i: Diarrhea, accessed online Nov. 2015 at: http://www.ipcrc.net/epco/EPEC-O%20M03a-q%20Symptoms/EPEC-O%20M03i%20Diarrhea/EPEC-O%20M03i%20Diarrhea%20PH.pdf
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 86.
- Fragkos, K. et al. What about clonidine for diarrhoea? A systematic review and meta-analysis of its effect in humans, Therapeutic Advance in Gastroenterology, 2016;9(3):282-301.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 843-850.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 115.
- Wanke, C. et al. Approach to the adult with acute diarrhea in resource-rich countries, UpToDate, literature review current through Nov. 2015.
- Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 267-273.

Dizziness & Vertigo

DEFINITION

Dizziness is a sensation of lightheadedness or feeling of faintness but without perception that the person or their surroundings are moving. Dizziness could be provoked by alterations of blood pressure or decreased cerebral blood flow.

Vertigo is a subtype of dizziness in which a person perceives a false sense of motion or spinning of their surroundings or themselves. Vertigo can arise in the brain, spinal cord, or due to problems in the inner ear.

CAUSES

- Disease States:
  - » Brain cancer/metastases, Multiple Sclerosis, stroke, heart disease, diabetes
- Other Conditions:
  - » Orthostasis, change in blood pressure, bradycardia, hypoglycemia, infections, migraine, dehydration, anxiety
- Medications:
  - » Antiepileptics, antidepressants, antihypertensives, anxiolytics, aminoglycosides, alcohol, diuretics, quinine, muscle relaxants, opioid analgesics
- Inner Ear Problems:
  - » Trauma, Meniere's Disease, vestibular neuritis, labryinthitis, nystagmus, tinnitus

HOW TO RECOGNIZE SYMPTOM

- Dizziness is more likely to be associated with maneuvers that alter blood pressure or decrease cerebral blood flow but tends not to worsen with head movement
  - » It can be associated with changes in blood pressure and heart rate, diaphoresis, hazy vision
- Vertigo is usually associated with the false sense of movement aggravated by movement of the head
  - » Room is spinning, sensation of falling, inability to walk or stand, need to hold on to things to move around
- Symptoms common to dizziness and vertigo
  - » Feeling of faintness, lightheadedness, weakness, falling, unsteady gait
  - » Can be associated with nausea/vomiting

CLINICAL INSIGHTS

- Feelings may last from seconds to days and may wax and wane depending on triggers
- Frequently assess antihypertensive use and determine if reduction is necessary
- To approach therapy:
  - » Attempt to differentiate between vertigo vs. dizziness
  - » Etiology guides proper treatment
  - » Identify triggers and accompanying symptoms
- Non-Pharmacologic Therapy:
  - » Reduce or remove offending agents, if possible (eg, any recent addition or dose increase of medication)
  - » Dizziness: Rest, lie down, hydrate
  - » Vertigo: Do not lie on your back, sit down to help relieve the spinning sensation; move slowly to avoid falling
  - » Educate patient to avoid sudden movements when getting sitting or standing up or down to avoid abrupt change of blood flow
- Pharmacologic Therapies:
  - » Treatment for dizziness is less specific
  - » Vertigo/dizziness, accompanying symptoms, underlying problem
  - » Vestibular Suppressants: anticholinergics, antihistamines, and benzodiazepines
  - » Other classes of medications that may provide benefit include: anti-inflammatories, anti-migraine (triptans), anticonvulsants, antidepressants, antiemetics

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICHOLINERGIC				
Scopolamine (Transderm-Scop)	Initial: 1.5mg patch applied Q 72 hours MDD: 1.5mg patch applied Q 72 hr	Transdermal patch: 1.5mg	• Used for vestibular-related symptoms • May contribute to undesirable anticholinergic effects in elderly such as dry mouth, agitation/delirium, and urinary retention • Does not work immediately; 6-8 hours until onset of action • Apply on clean, dry, hairless skin behind ear	NA
ANTIHISTAMINE				
Dimenhydrinate (Dramamine)	Initial: 50-100mg Q4-6h MDD: 400mg/day	Chewable tablet: 50mg Solution for injection: 50mg/ml Tablet: 50mg	• Used for vertigo, nausea, and vomiting associated with motion sickness. • Side effects: tachycardia, excitation, restlessness	Y
Diphenhydramine (Benadryl)	Initial: 25mg – 50mg PO QID MDD: 300mg/day	Capsule: 25mg, 50mg Oral solution: 12.5mg/5ml Solution for injection: 50mg/ml Tablet: 25mg, 50mg	• Used for vertigo, nausea, and vomiting associated with motion sickness. • Useful if sedation is necessary • Avoid in elderly or demented patients due to anticholinergic adverse effects • Antihistamine with mildly anxiolytic, analgesic, and sedative properties • Also useful for itching	Y
Hydroxyzine (Vistaril)	Initial: 25mg QID MDD: 400mg/day	Capsule (pamoate): 25mg, 50mg, 100mg Oral solution: 25mg/ml, 50mg/ml Tablet (HCl): 10mg, 25mg, 50mg	• Used for vertigo, nausea, and vomiting associated with motion sickness. • Sedating • Antihistamine with anxiolytic properties	Y
Meclizine (Antivert)	Initial: 25-100mg/day in divided doses MDD: 100mg/day	Chewable tablet: 25mg Tablet: 12.5mg, 25mg, 32mg, 50mg	• Used for vertigo associated to problems relating to the vestibular system • May contribute to undesirable anticholinergic effects in elderly such as dry mouth, agitation/delirium, and urinary retention • Chewable tablets may be admin with or without water, or swallowed whole with water • Onset of action is 1 hour and effects may last from 8-24 hours	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BENZODIAZEPINES				
Diazepam (Valium)	Initial 2-10mg PO Q6-8H MDD: not established for this indication	Oral solution: 5mg/ml Solution for injection: 5mg/ml Tablet: 2mg, 5mg, 10mg	• Used for vertigo associated to problems relating to vestibular system • May increase dose based on response for severe vertigo • Can be given IV; PO:INJ is 1:1 • Long acting, active metabolites may accumulate and contribute to sedation • Most rapid onset of action with single dose • Rapid onset • Oral solution is more expensive than tablets	Y
Lorazepam (Ativan)	Initial 0.5-2mg Q4-8 hours MDD: not established for this indication	Oral solution: 2mg/ml Solution for injection: 2mg/ml, 4mg/ml Tablet: 0.5mg, 1mg. 2mg	• Used for vertigo associated to problems relating to vestibular system • Can be given IV/IM; PO:INJ is 1:1 • Short acting; Intermediate onset • No active metabolites • Oral Concentrate is more expensive than tablets	Y
ANTIEMETIC				
Prochlorperazine (Compazine)	Initial (PO): 5mg TID MDD(PO): 30mg/day Initial (PR): 25mg TID MDD (PR): 75mg/day	Suppository: 25mg Tablet: 5mg, 10mg	• Used for vertigo in labyrinthine disorders • Side Effects: Anticholinergic side effects, photosensitivity, extrapyramidal reactions, drowsiness • Gradually reduce to 5mg QD-BID, if possible • Useful if patient also has nausea symptoms	Y
Promethazine (Phenergan)	Initial: 12.5-25mg PO/ PR q4-12 hours MDD: Not established for this indication	Suppository: 25mg Tablet: 25mg	• Used for vertigo, nausea, and vomiting associated with motion sickness • May lower seizure threshold • May prolong QT interval • Sedating	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CORTICOSTEROID				
Dexamethasone (Decadron)	Initial: 4-8mg QAM MDD: Variable	Oral solution: 0.5mg/5ml, 1mg/ml Tablet: 0.5mg, 0.75mg, 1mg, 1.5mg, 2mg, 4mg, 6mg	• Used for elevated intracranial pressure (ICP) • Dexamethasone should not be d/c abruptly and instead tapered over 1-4 weeks depending on dose • May cause psychiatric disturbances, mood swings, and seizures • May cause fluid retention, hypertension, arrhythmias, insomnia, GI perforation risk	Y
ORTHOSTASIS				
Fludrocortisone (Florinef)	Initial: 0.1-0.2mg QAM MDD: 1mg/day	Tablet: 0.1mg	• May be suitable for patients experiencing symptoms related to orthostatic hypotension • May raise upright systolic blood pressure, while affecting supine blood pressure • Use caution in patients with heart failure or recent MI • Doses greater than 0.3mg/day may have unwanted side effects (hypertension, hypokalemia) and may not be beneficial	Y
Midodrine (Amatine)	Initial: 10mg TID with doses given every 3-4 hours and final dose not later than 6PM MDD: 40mg/day	Tablet: 2.5mg, 5mg, 10mg	• May be suitable for patients experiencing symptoms related to orthostatic hypotension • Dose reduced in renal impairment: 2.5mg TID • Contraindicated if acute renal failure	Y

References

- Baloh RW. Approach to the evaluation of the dizzy patient. Otolaryngol Head Neck Surg. 1995; 112:3-7.
- Baloh RW. Differentiating between peripheral and central causes of vertigo. Otolaryngol Head Neck Surg 1998; 119:55-59.
- Bhattacharyya N, Baugh RF, Orvidas L, et al. Clinical practice guideline: benign paroxysmal positional vertigo. Otolaryngol Head Neck Surg 2008; 139:S47-S81.
- Branch, W. et al. Approach to the patient with dizziness, UpToDate, literature review current through Nov. 2015.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 204-208.
- Furman, J. et al. Treatment of Vertigo, UpToDate, literature review current through Nov. 2015.
- Hotson JR, Baloh RW. Acute vestibular syndrome. N Engl J Med 1998; 339:680-685.
- Kerber KA. Vertigo and Dizziness in the Emergency Department. Emerg Med Clin North Am. 2009 Feb; 27(1): 39–viii.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Sloane PD, Dallara J, Roach C, et al. Management of dizziness in primary care. J Am Board Fam Pract 1994; 7:1
- Swartz, R. et al. Treatment of vertigo, American Family Physician, 2005, Vol.71, No. 6.
- Tucci D. Dizziness and Vertigo. Merck Manuals, Professional Version. Accessed August 13, 2015. Available at http://www.merckmanuals.com/professional/ear-nose-and-throat-disorders/approach-to-the-patient-with-ear-problems/dizziness-and-vertigo
- Yacovino, D. et al. Pharmacologic treatment of vestibular disorders, Vestibular Disorders Association, accessed online Nov. 2015 at: https://vestibular.org/sites/default/files/page_files/Documents/Pharmacologic%20treatments.pdf

Dyspepsia & GERD

DEFINITION

Dyspepsia is a chronic feeling of heartburn, burping, bloating, and stomach pain usually after eating. It involves delayed gastric emptying, impaired gastric accommodation to a meal, and abnormal intestinal motility. A burning sensation may radiate to neck or arms.

GERD (Gastroesophageal Reflux Disease) is a condition that causes bothersome symptoms such as heartburn or regurgitation due to reflux of stomach contents into the esophagus.

Etiology of GERD is the abnormal reflux of gastric contents from the stomach into the esophagus.

CAUSES

Dyspepsia and GERD:

- Diet
  - » Caffeine, alcohol, chocolate, coffee/cola/tea, fatty meals, spicy foods, acidic foods, carbonated beverages
- Eating quickly or too much
- Smoking
- Medications
  - » Bisphosphonates, codeine, iron, metformin, NSAIDs, potassium, corticosteroids, theophylline, vitamin D, aspirin, digoxin, antibiotics, quinidine
- Medical Conditions:
  - » Gastroparesis, peptic ulcer disease, biliary tract disease, gastric or esophageal cancer/obstruction, ascites, Helicobater Pylori (*H. Pylori*)

Dyspepsia:

- Additional medications: quinidine
- Stress

GERD:

- Additional medications: anticholinergics, tricyclic antidepressants, calcium channel blockers, nitrates, opioids, sedatives
- Defective lower esophageal sphincter
- Conditions that reduce gastrointestinal motility

HOW TO RECOGNIZE SYMPTOM

Dyspepsia and GERD:

- Common Symptoms: heartburn, belching, bloating, nausea, vomiting, hypersalivation, regurgitation, acidic or sour taste in mouth, upper abdominal discomfort/pain, dysphagia, bleeding, chest pain

Dyspepsia:

- Early satiety
- Intolerance to certain foods or drinks

GERD:

- Esophageal related symptoms: cough, laryngitis, asthma, dental erosions, abdominal pain, burning in through
- Other: sinusitis, pulmonary fibrosis, pharyngitis, otitis media

CLINICAL INSIGHTS

- Lifestyle Modifications:
  - » Sleep with head elevated 30-45 degree
  - » Avoid eating 2-3 hours before bedtime
  - » Remain upright after meals
- Antacids:
  - » The fastest acting medications and used for intermittent symptoms (less than 2 times per week)
  - » Antacids can be used as needed in conjunction with Proton Pump Inhibitors (PPIs) or Histamine-2 receptor Antagonists (H2RA)
  - » Caution with drug interactions (could decrease absorption of certain medications such as floroquinolone antibiotics)
  - » Doses of aluminum/magnesium containing antacids of more than 100-200ml per day are more likely to cause diarrhea as the laxative effect of magnesium exceeds the constipating effect of aluminum
- Proton Pump Inhibitors:
  - » Complications of chronic PPI's include pneumonia, risk of fractures, *Clostridium difficle*, hypomagnesemia, altered absorption of concomitantly administered drugs

- » Headache is a common side effect of all PPIs
- » Medication choice should be based on onset of action, adverse effect, and cost
- » At starting doses all PPI's are similar in efficacy; omeprazole shows an increased benefit as the dose is increased

PPI EQUIVALENCY

ESOMEPRAZOLE	LANSOPRAZOLE	OMEPRAZOLE	PANTOPRAZOLE	RABEPRAZOLE	DEXLANSOPRAZOLE
20-40mg	30mg	20mg	40mg	20mg	60mg

Dyspepsia:

- Symptoms may present with similar symptoms include GERD, biliary tract disease, pancreatitis, or irritable bowel syndrome

GERD:

- Typical treatment for GERD is 4-8 weeks. Monitor treatment and discontinue when appropriate; consider periodic attempts at discontinuation
- Chronic acid-suppression therapy with a PPI should only be considered with continuous symptoms
- Treatment:
  - » Intermittent/mild heartburn:
    - ° Lifestyle modifications + Antacids
  - » Moderate-Severe Symptoms/Symptomatic GERD Relief/Erosive Esophagitis:
    - ° Lifestyle modifications + PPI or H2-receptor antagonist
  - » PPI's are the most effective agents for healing the gastric mucosa compared to other therapies
  - » Promotility therapy is generally not recommended as monotherapy
  - » PPI's are not meant to be used on an "as-needed" basis; they must be used continuously for relief
  - » H2-receptor antagonists and antacids are better choices for fast symptomatic relief
- Although not commonly performed in the hospice setting, may consider testing for *H. Pylori* infection
  - » If confirmed, treatment is based on American College of Gastroenterology Guidelines

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
PROTON PUMP INHIBITORS				
Dexlansoprazole (Dexilant)	Initial: 30mg QD MDD: 60mg/day	Capsule (DR): 30mg, 60mg	• If needed, can open capsule and mix with apple sauce • Doses greater than 30mg does not provide benefit during maintenance therapy • Duration GERD treatment: 4 weeks • Expensive	Y
Esomeprazole (Nexium)	Initial: 20mg – 40mg PO/IV QD MDD: 40mg/day	Capsule (DR): 20mg, 40mg Packet: 40mg Solution for injection: 20mg, 40mg	• Max dose for patients with severe liver disease is 20mg • If needed, can open capsule and mix with apple sauce/ juice • Duration GERD treatment: 4 weeks • Expensive	Y
Lansoprazole (Prevacid)	Initial: 15mg PO/SL QD MDD: 30mg/day	Capsule (DR): 15mg, 30mg Oral disintegrating tablet (ODT)*: 15mg, 30mg Oral suspension: 15mg/packet, 30mg/packet Solution for injection: 30mg	• Capsules may be opened and intact contents added to soft food for immediate administration. • Oral disintegrating tablets should be placed intact on tongue until particles can be swallowed. Alternatively, they can be placed in an oral syringe with 4ml or 10ml water (4ml for 15mg tablet, 10ml for 30mg tablet) and administered within 15min of tablet dissolution. Additional water can be used to administer any remaining in the syringe. • Duration of GERD treatment: 8 weeks • Expensive	Y/N*
Omeprazole (Prilosec)	Initial: 20mg PO QD MDD: 40mg/day	Capsule (DR): 10mg, 20mg, 40mg Oral suspension: 2mg/ml Packet: 2.5mg, 10mg Tablet (DR)*: 20mg	• OTC tablet available • If needed, can open capsule and mix with apple sauce/juice • Duration GERD treatment: 4 weeks *(Continued on next page)*	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
PROTON PUMP INHIBITORS (CONTINUED)				
Pantoprazole (Protonix)	Initial: 40mg PO/IV QD MDD: 40mg/day	Packet: 40mg Solution for injection: 40mg Tablet (DR): 20mg, 40mg	• Duration GERD treatment: 4 weeks	N
Rabeprazole (Aciphex)	Initial: 20mg QD MDD: 20mg/day	Sprinkle capsule (DR): 5mg, 10mg Tablet (EC)*: 20mg	• If needed, sprinkle capsules may be opened and contents added to soft food for administration within 15min • Take after morning meal • Duration GERD treatment: 4-8 weeks, maintenance therapy recommended • Expensive	Y/N*
H2 – ANTAGONIST				
Cimetidine (Tagamet)	Initial: 400mg PO QID or 800mg BID, 200mg PO BID (OTC) MDD: 2,400mg/day	Oral solution: 300mg/5ml Tablet: 200mg, 300mg, 400mg, 800mg	• Many drug interactions; Avoid USE • Prolonged use is associated with rare development of gynecomastia • Liquid is expensive	Y
Famotidine (Pepcid)	Initial: 20mg BID for up to 6 weeks MDD: 80mg/day	Oral suspension: 40mg/5ml Tablet: 10mg, 20mg, 40mg	• Take at bedtime • May take with antacids, if needed (combination products available) • CrCl < 50ml/min, ½ the dose • Liquid is expensive	Y
Nizatidine (Axid)	Initial: 150-300mg QD MDD: 300mg/day	Capsule: 150mg, 300mg Oral solution: 15mg/5ml Tablet: 75mg	• Liquid is expensive	Y
Ranitidine (Zantac)	Initial: 75-150mg PO QD-BID MDD: 300mg/day	Capsule: 150mg, 30mg Syrup: 15mg/ml Tablet: 75mg, 150mg, 300mg	• Well tolerated • CrCl < 50ml/min: Max dose is 150mg QD • CrCl < 10ml/min: Max dose is 75-150mg QD • Liquid is expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTACIDS				
Aluminum & Magnesium Hydroxide (Maalox/ Mylanta)	Initial: 10-20ml QID MDD: 80ml/day (200mg/5ml), 45ml/day (500mg/5ml)	Oral suspension: Aluminum 200mg and Magnesium 200mg/5ml	• Avoid in patients with renal insufficiency due to potential for adverse effects due to magnesium and/or aluminum accumulation due to reduced clearance • Side Effects: constipation (aluminum), diarrhea (magnesium); with doses greater than 100-200ml/24h or more the laxative effect of magnesium may override the constipating effect of aluminum	Y
Aluminum & Magnesium Hydroxide & Simethicone (Maalox Plus)	Initial (tabs): 1-4 tabs PO QID Initial (liquid): 10-20ml between meals and at bedtime MDD: 12-16 tabs/day, 80-120ml/day (200mg/200mg/20mg liquid), 40-60ml/day (400mg/400mg/40mg liquid)	Oral suspension: 200/200/25mg/ 5ml Tablet: 225mg Aluminum Hydroxide/200mg Magnesium Hydroxide/25mg Simethicone	• Avoid in patients with renal insufficiency due to potential for adverse effects due to magnesium and/or aluminum accumulation due to reduced clearance • Side Effects: constipation (aluminum), diarrhea (magnesium); with doses greater than 100-200ml/24h or more the laxative effect of magnesium may override the constipating effect of aluminum	Y
Calcium Carbonate (Tums)	Initial: 1-4 tabs as symptoms occur MDD: 8,000mg/day	Capsule: 364mg, 1,250mg Chewable tablet: 420mg, 500mg, 750mg, 1,000mg Powder: 1,000mg/packet Tablet: 500mg, 600mg, 1,250mg	• May cause constipation • Do not use maximum dosage for longer than 2 weeks • Use cautiously in patients with renal insufficiency	Y
Sodium Bicarbonate	Initial: <60 y.o.: 325mg to 1,300mg 1-4 times/day, MDD: 7,800mg/day Initial: >60 y.o.: 325-650mg every 4 hours, MDD: 900mg/day	Tablet: 325mg, 648mg, 650mg	• May cause metabolic alkalosis	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTI-GAS				
Simethicone (Gas-X, GasAid, Mytab Gas, Gas Relief, Phazyme)	Initial: 40-125mg PO QID after meals and at bedtime MDD: 500mg/day	Chewable tablet: 80mg, 125mg Oral disintegrating strip: 40mg, 62.5mg Oral suspension: 40mg/0.6ml, 20mg/0.3ml Softgel:125mg, 166mg, 180mg	• Useful treatment for gas related discomfort	Y
PRO-MOTILITY				
Bethanechol (Urecholine)	Initial: 25mg QID MDD: Not established for this indication	Tablet: 5mg, 10mg	• Cholinergic agonist • Side Effects: diarrhea, abdominal cramping, and blurred vision • Take 1 hour before or 2 hours after meals	Y
Metoclopramide (Reglan, Metozolv ODT)	Initial: 10-15mg PO QID 30 minutes before meals and at bedtime MDD: 60mg/day	Solution for injection: 5mg/ml Syrup: 5mg/5ml Tablet: 5mg, 10mg	• Give 30 minutes before a meal • Do not use for longer than 3 months • Avoid use in Parkinson patients • Watch for extrapyramidal symptoms, agitation • Max dose renal patients 20mg/day	Y
OTHER				
Misoprostol	Initial: 100-200mcg TID and QHS MDD: 800mg/day	Tablet: 100mcg, 200mcg	• Take with food to avoid GI side effects • Significant GI side effects, including diarrhea, nausea, vomiting, and abdominal cramps • Avoid antacids with magnesium while taking this medication	Y
Sucralfate	Initial: 1g BID MDD: Not established for this indication	Oral suspension: 1g/10ml Tablet: 1g	• GERD is an off labeled use • Take on an empty stomach • May cause constipation • Do not take antacids within 30 minutes of taking this drug	Y

References

- American Gastroenterological Association Institute. Medical position statement on the management of gastroesophageal reflux disease. Gastroenterology 2008;135:1383–91.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 664.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 218,253-254.
- DeVault KR, Castell DO, American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 2005; 100:190-200.
- Fass, R. et al. Approach to refractory gastroesophageal reflux disease in adults, UpToDate, literature review current through Nov. 2015.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 821-5.
- Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Institute. Technical review on the management of gastroesophageal reflux disease. Gastroenterology 2008; 135:1392-413.
- Kahrilas, P. et al. Medical management of gastroesophageal reflux disease in adults, UpToDate, literature review current through Nov. 2015.
- Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 2013; 108:308-328.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Longstreth, G. et al. Functional dyspepsia in adults, UpToDate, literature review current through Nov. 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 123.
- Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 274-283.

Dyspnea

DEFINITION

A subjective feeling of breathing discomfort that results when there is an imbalance between the perceived need to breathe and the ability to do so.

CAUSES

- Caused by complex interactions of physical, psychological, social, and environmental factors
- Nearly any terminal disease can potentially cause dyspnea, particularly in the end-stages
- Lung diseases / conditions:
  - » Chronic Obstructive Pulmonary Disease (COPD)
  - » Bronchial obstruction due to lung cancer or cancer with lung metastases
  - » Interstitial lung disease / pulmonary fibrosis
  - » Cystic fibrosis
  - » Bronchospasm
  - » Pleural or pericardial effusion
  - » Infection (pneumonia)
  - » Pulmonary embolism
  - » Thick pulmonary secretions
  - » Pulmonary edema or ascites
- Other organ failure (heart, liver and kidney)
- Other non-lung cancers
- Neuromuscular diseases, particularly Amyotrophic Lateral Schlerosis (ALS)
- Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS)
- Mechanical causes
- Uncontrolled symptoms (Anxiety, Pain, Cough)
- Obesity
- Anemia
- Cachexia
- Exertion
- Improper positioning (eg, orthopnea)
- Environmental causes such as dust, pollen, dander, etc.
- Cigarette smoking

HOW TO RECOGNIZE SYMPTOM

- Complaint of breathing difficulties (smothering, chest tightness)
- Inability to speak in complete sentences due to running out of breath
- Panic, fear, and anxiety are common
- Cyanosis
- Increased use of accessory muscles
- May consider use of the Visual Analog Scale (VAS) or the Modified Borg Scale to assess for dyspnea
- For non-verbal patients, changes from baseline characteristics / behaviors may be observed, including tachypnea, gasping, anxiety, restlessness, and agitation

CLINICAL INSIGHTS

- When possible, identify and direct treatment at underlying causes (**Table 1**)
- Tachypnea (respiratory rate > 20/min) is not the same as dyspnea; patients may be dyspnic with a normal respiratory rate and patients with tachypnea may not report the subjective feeling of dyspnea

TABLE 1 – UNDERLYING CAUSES OF DYSPNEA AND POTENTIAL TREATMENT APPROACHES

UNDERLYING CAUSE	TREATMENT APPROACHES
COPD	Oxygen Optimize bronchodilator regimen* +/- Low dose opioid and/or benzodiazepine +/- Oral steroid
Cardiac disease, esp. CHF	Oxygen Add or titrate diuretics if edema present The oral route of diuretics becomes ineffective during exacerbations of heart failure +/- Low dose opioid and/or benzodiazepine Standard heart failure therapies such as ACE-inhibitors also provide symptomatic benefit Note: bronchodilators are not effective in the absence of acute or chronic lung disease.
Poorly controlled symptoms (ex: pain, cough)	See respective chapters on pain and cough management
Dyspnea with anxiety component	Benzodiazepines
Thick mucus / secretions	Mucolytics – See chapter on secretion management
Edema	Diuretics Reduce or discontinue artificial feedings / IV hydration
Infection	Consider antibiotics if goal of use is symptom reduction Opioids, benzodiazepines, and bronchodilators can be used for symptom relief
Chronic pulmonary emboli	Anticoagulation is reasonable if the goal of use is symptom reduction Opioids and benzodiazepines can be used for symptom relief

* The OPPC recommended bronchodilator regimen for optimal control of end-stage COPD symptoms is albuterol/ipratropium nebs four times daily plus albuterol nebs every 4 hours as needed.

- Opioids
  - » Although morphine is most commonly used for dyspnea, no opioid has been shown to be superior
    - ° Methadone is not recommended for the treatment of dyspnea
  - » Most extensively studied drug class for treatment of dyspnea in advanced illness
  - » Generally, lower doses of opioids are needed to manage dyspnea versus pain
  - » When using for dyspnea, establish an effective dose using the immediate-release formulations, and then consider an extended-release formulation if warranted
  - » When titrated against the symptom burden of the patient, opioids will rarely, if ever, result in fatal respiratory depression, even in patients at risk for respiratory depression such as those with ALS
  - » There is only conflicting evidence to support the use of inhaled opioids for dyspnea
    - ° They should be reserved for patients who do not respond to other routes of administration.
    - ° Bronchospasm is a possible adverse effect with inhaled opioids; this risk is reduced by using preservative-free solutions for injection
    - ° Oral opioid solutions should not be used for inhalation
- Benzodiazepines
  - » Use when there is an anxiety component to dyspnea
  - » Lorazepam is the drug of choice in the hospice setting
  - » Often, both opioids and benzodiazepines are needed for optimal symptom management
  - » For frequent or persistent symptoms, consider a long-acting benzodiazepine, such as clonazepam
- Bronchodilators
  - » Drugs of choice for dyspnea due to lung disease
  - » Not typically effective in patients without lung disease or acute pulmonary conditions
  - » The nebulized route is preferred over dry-powder inhalers (DPIs) or metered dose inhalers (MDIs) in patients with end-stage lung disease or patients with limited coordination / cognition to ensure optimal drug delivery and symptom control

    - If unsure about patients' abilities to effectively use, recommend directly observed therapy and technique evaluation
    - If an MDI must be used, a spacer can greatly improve drug delivery and symptom control
  - Duplicate therapy within the same therapeutic class of bronchodilator (eg, routine use of multiple beta-2 agonists) is not more effective, but is associated with increased adverse effects
  - Side effects, including anxiety, tremor, and agitation may actually worsen symptoms, particularly if the recommended dose is exceeded or with duplicate therapy

- Diuretics
  - Drugs of choice for edema due to fluid overload
  - Consider monitoring electrolytes if consistent with plan of care
  - There is only conflicting evidence to support the use of inhaled furosemide
    - Use should not be considered first line therapy
    - Theorized mechanisms of action include suppressing pulmonary C-fibers and stimulating pulmonary stretch receptors; beneficial effect, if any, is not due to diuresis.
- Oxygen
  - Most beneficial to improve exertional dyspnea; less likely to be beneficial in the terminal phase
  - Although patients with O2 saturations of < 90% are frequently dyspnic, O2 saturations should not be solely relied on for assessing dyspnea, as some patients may not be dyspnic at rest, despite low saturation
  - In many cases, routine monitoring of O2 saturations is not beneficial; goals of O2 therapy should be defined so that benefits can be weighed against burdens of use
  - Confused or distressed patients may feel restricted with O2 administration and may not tolerate; a nasal cannula may be preferred over a mask to enable communication and feeding
- Corticosteroids
  - Consider if inflammatory component to dyspnea
  - Oral steroids are typically preferred over inhaled steroids at the end of life
    - May also increase mood, sense of well-being, and appetite
    - Symptomatic benefits of oral therapy typically outweigh long-term risks (ie, increased risk of infection, osteoporosis) during end of life care symptom management
- Non-pharmacological interventions should be considered for all patients
  - Ask the patient yes or no questions to limit their need to expend energy responding to questions
  - Seated position with adequate support of head, neck, and arms with pillows is preferred
  - Avoid foods and beverages that contribute to abdominal distension (gas-forming foods / carbonated beverages)
  - Provide increased air-movement and moistened air with use of fans and/or humidifiers

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OPIOIDS				
Fentanyl (Sublimaze)	Initial: 25-50mcg IV/SQ/nebulized* Q2-4 hours PRN MDD: None	Solution for injection: 50mcg/ml	• Protect vials from light to prevent loss of potency • *NOTE: there is only conflicting evidence to support the use of inhaled opioids for dyspnea; reserve use for when other routes have failed. • Do not exceed 100mcg/nebulized dose	-
Hydromorphone (Dilaudid)	Initial (PO/SL/PR): 1mg Q4 hours PRN Initial (SQ/IV): 0.25mg Q4 hours PRN Initial (nebulized)*: 4mg / SVN Q4 hours PRN MDD: None	Oral solution: 1mg/ml Solution for injection: 2mg/ml Tablets: 2mg, 4mg, 8mg	• Preferred over morphine for patients with renal impairment • *NOTE: there is only conflicting evidence to support the use of inhaled opioids for dyspnea; reserve use for when other routes have failed. • Although commonly ordered by the sublingual route in the hospice setting, there is no evidence that substantial sublingual absorption occurs; in fact retaining in the mouth may delay onset	Y
Morphine Sulfate (MSIR, Roxanol, MSContin)	Initial (PO/SL/PR): 2.5-5mg Q4 hours PRN Initial (SQ/IV): 1-2mg Q4 hours PRN Initial (nebulized)*: 2-5mg / SVN QID PRN MDD: None	Oral solution: 10mg/5ml, 20mg/5ml, 20mg/ml Soluble tablets: 10mg Solution for injection: 10mg/ml, 15mg/ml Tablets (MSIR): 15mg, 30mg	• Most comprehensively studied opioid for treatment of dyspnea • Avoid chronic dosing in patients with renal impairment • *NOTE: there is only conflicting evidence to support the use of inhaled opioids for dyspnea; reserve use for when other routes have failed. • Although commonly ordered by the sublingual route in the hospice setting, there is no evidence that substantial sublingual absorption occurs; in fact retaining in the mouth may delay onset	Y
Oxycodone (OxyIR, Oxycontin)	Initial: 2.5-5mg PO/SL/PR Q4 hours PRN MDD: None	Oral solution: 20mg/ml Tablets: 5mg, 10mg, 15mg, 20mg, 30mg	• Preferred over morphine for patients with renal impairment • Although commonly ordered by the sublingual route in the hospice setting, there is no evidence that substantial sublingual absorption occurs; in fact retaining in the mouth may delay onset	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BENZODIAZEPINES				
Alprazolam (Xanax, Niravam)	Initial: 0.25-0.5mg PO/SL/PR QID PRN MDD: Not established for this indication	Oral solution: 1mg/ml Tablets (IR): 0.25mg, 0.5mg, 1mg, 2mg Tablets (ODT): 0.25mg, 0.5mg, 1mg, 2mg Tablets (XR)*: 0.5mg, 1mg, 2mg, 3mg	• Short duration of action can lead to abrupt wearing off and potentially worsening dyspnea in a cyclical fashion • Avoid or reduce dose in patients with liver disease • Most likely benzodiazepine to cause psychological dependence • May produce paradoxical agitation or worsen existing agitation in dementia patients	Y/N*
Clonazepam (Klonopin)	Initial: 0.25mg PO BID PRN MDD: Not established for this indication	Tablets (IR): 0.5mg, 1mg, 2mg Tablets (ODT): 0.125mg, 0.25mg, 0.5mg, 1mg, 2mg	• Long-acting effect on dyspnea • Use with caution in elderly or patients with renal impairment due to active metabolite • Contraindicated with significant hepatic impairment • May produce paradoxical agitation or worsen existing agitation in dementia patients	Y
Diazepam (Valium)	Initial: 2-10mg PO/SL/PR/IV BID-QID MDD: Not established for this indication	Oral solution: 1mg/ml, 5mg/ml Solution for injection: 5mg/ml Tablets: 2mg, 5mg, 10mg	• Long-acting effect on dyspnea • Use with caution in elderly or patients with renal or hepatic impairment due to active metabolite and extended duration of action • May produce paradoxical agitation or worsen existing agitation in dementia patients	Y
Lorazepam (Ativan)	Initial: 0.25-0.5mg PO/SL/SQ/IV QID PRN MDD: Not established for this indication	Oral solution: 2mg/ml Solution for injection: 2mg/ml, 4mg/ml Tablets: 0.5mg, 1mg, 2mg	• Intermediate acting benzodiazepine • Rapidly absorbed sublingually • Poorly absorbed rectally; not recommended by this route • Avoid or reduce dose in patients with liver disease • May produce paradoxical agitation or worsen existing agitation in dementia patients	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BRONCHODILATORS				
Albuterol (ProAir, Ventolin)	Initial (MDI): 2 puffs Q4-6H PRN MDD (MDI): 12 inhalations/day Initial (nebulizer): 2.5mg 3 to 4 times daily as needed; Quick relief: 1.25 to 5mg every 4 to 8 hours as needed MDD (nebulizer): Not established	Metered dose inhaler (MDI): 90mcg/actuation Solution for nebulization: 0.083% (3ml), 0.63mg/3ml (3ml), 0.5% (20ml)	• Drug of choice for acute dyspnea due to pulmonary disease • Nebulized route preferred • May cause anxiety, agitation, and tremor as adverse effects	-
Albuterol/Ipratropium (Combivent, DuoNeb)	Initial (MDI): 1 inhalations QID Initial (nebulizer): 3ml Q6H MDD (MDI): 12 inhalations/day MDD (nebulizer): 3ml Q4H	Metered dose inhaler (MDI): 0.09mg/0.018mg Solution for nebulization: 3mg/3ml	• Drug of choice for maintenance symptoms of dyspnea due to COPD • Nebulized route preferred	-
Ipratropium Bromide (Atrovent)	Initial (MDI): 2 inhalations QID MDD (MDI): 12 inhalations/day Initial (nebulizer): 500mcg Q6-8H MDD (nebulizer): 12 puffs or 6 nebs/ day	Metered dose inhaler (MDI): 17mcg/actuation (12.9 g) Solution for nebulization: 0.02% (500mcg/2.5ml)	• This nebulizer mixed with albuterol nebulizer is stable for 1 hour • Mixing ipratropium and albuterol separately is more expensive than the commercially available combination	-
Levalbuterol (Xopenex)	Initial (MDI): 1-2 puffs Q4-6 hours PRN MDD (MDI): 12 inhalations/day Initial (nebulizer): 0.63mg / SVN TID MDD (nebulizer): 3.75mg/day	Metered dose inhaler (MDI): 45mcg/actuation Solution for nebulization: 0.31mg/3ml, 0.63mg/3ml, 1.25mg/3ml	• Consider if documented intolerance to albuterol • Nebulized route preferred • May cause anxiety, agitation, and tremor as adverse effects • Nebulizer solutions are expensive	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CORTICOSTEROIDS				
Dexamethasone (Decadron)	Initial: 2-16mg PO/ SQ/IV BID MDD: 40mg/day PO/SQ/IV	Oral solution: 0.5mg/5ml, 1mg/ml Solution for injection: 4mg/ml, 10mg/ml Tablet: 0.25mg, 0.5mg, 0.75mg, 1mg, 1.5mg, 2mg, 4mg, 6mg	• Causes less sodium/water retention than prednisone • Use with caution in diabetics; may increase blood glucose levels • GI upset is a potential adverse effect • Give last dose by 2pm to avoid steroid induced insomnia	Y
Prednisone (Orasone)	Initial: 5-80mg PO/ SQ/IV daily MDD: 80mg/day	Oral solution: 1mg/ml, 5mg/ml Tablet: 1mg, 2.5mg, 5mg, 10mg, 20mg, 50mg	• Use with caution in diabetics; may increase blood glucose levels • GI upset is a potential adverse effect • Give last dose by 2pm to avoid steroid induced insomnia	Y
DIURETICS				
Furosemide (Lasix)	Initial (PO/SQ/IV/IM): 20-40mg QD Initial (nebulizer)*: 20mg QID (using solution for injection) MDD (PO/SQ/IV/IM): Not established for this condition MDD (nebulizer)*: 200mg/day Initial (oral solution, tablets): Not established	Oral solution: 40mg/5ml, 10mg/ml Solution for injection: 40mg/4ml Tablet: 20mg, 40mg, 80mg	• Drug of choice for dyspnea due to fluid retention • Monitor for electrolyte loss if consistent with plan of care • Other loop diuretics may be considered: 40mg furosemide = 1mg bumetanide = 20mg torsemide = 50mg ethacrynic acid • Dilute solution for injection limits dosing by SQ routes; use multiple sites if necessary; limit volume per dose to < 2.5ml • *NOTE: There is only conflicting evidence to support the use of inhaled furosemide for dyspnea; reserve use for when other routes / therapies have failed. • Parenteral route usually required for dyspnea due to exacerbation of heart failure	Y

References

- Boyden, J. et al. Nebulized medications for the treatment of dyspnea: a literature review, Journal of Aerosol Medicine and Pulmonary Drug Delivery, Vol. 28, No. 1, 2015.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 655-62,938-40,915-6,997.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 224-229.
- Dudgeon, D. et al. Assessment and management of dyspnea in palliative care, UpToDate, literature review current through Nov. 2015.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3j: Dyspnea, accessed online Nov. 2015 at: http://www.ipcrc.net/epco/EPEC-O%20M03a-q%20Symptoms/EPEC-O%20M03j%20Dyspnea/EPEC-O%20M03j%20Dyspnea%20PH.pdf
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 48.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 422-3,471,1107-30,1186-9,1232-7,1241-5,1259,1268-70.
- Jennings AL, Davies AN, Higgins JPT, Broadley K. Opioids for the palliation of breathlessness in terminal illness. Cochrane Database System Rev 2001:CD002066
- Krajnik M, Mousa SA, Stein C, et al. Opioid receptors and endogenous opioids in human lung tissue. Proceedings of the 11th World Congress on Pain, Sydney, Australia, 2005:419.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Mahler DA. Understanding mechanisms and documenting plausibility of palliative interventions for dyspnea, Curr Opin Support Palliat Care. 2011 Jun;5(2):71-6. Review.
- Owens, D. et al. Nebulized furosemide for the treatment of dyspnea, Journal of Hospice and Palliative Nursing, Vol.11, No.4, 2009.
- Peiffer C, Poline J, Thivard L, et al. Neural substrates for the perception of acutely induced dyspnea. Am J Respir Crit Care Med 2001; 163:951–957.
- Polosa R, Simidchiev A, Walters EH. Nebulised morphine for severe interstitial lung disease. Cochrane Database System Rev 2002:CD002872.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 196-198,339.
- Schwartzstein, R. et al. Approach to the patient with dyspnea, UpToDate, literature review current through Nov. 2015.
- Zebraski SE, Kochenesh SM, Raffa B. Lung opioid receptors: pharmacology and possible target for nebulised morphine in dyspnea. Life Sci 2000; 66:221–231.

Edema (Peripheral)

DEFINITION

It is an excessive buildup of fluid in the distal extremities (face, ankles, and feet) which may lead to swelling and discomfort.

CAUSES

- This is often a nonspecific finding that is common to many diseases.
- It is caused by increase in interstitial fluid volume, increased capillary permeability, and hypervolemia due to sodium and water retention
- Medical Conditions:
  - » Cardiac:
    - ° Heart failure
    - ° Pericarditis
    - ° Venous Thromboembolism (DVT/PE)
    - ° Cardiomyopathy
    - ° Tricuspid valve disease
  - » Renal
    - ° Renal failure (acute and renal)
  - » Liver
    - ° Liver failure
    - ° Cirrhosis
  - » Cancer
  - » Decreased Protein
    - ° Hypoalbuminemia
    - ° Malnutrition
    - ° Malabsorption
    - ° Nephrotic syndrome
  - » Hyponatremia
  - » Infections
  - » Allergic reactions
  - » Myxedema
  - » Lymphedema
- Medications
  - » NSAIDs
  - » Corticosteroids
  - » Non-dihydropyridine calcium channel blockers
    - ° Diltiazem
  - » Cyclosporine
  - » Pramiprexole
  - » Gabapentin
  - » Pioglitazone
  - » Vasodilators (hydralazine, minoxidil)
  - » Beta-blockers
- Radiation therapy effects
- Immobility
- Idiopathic

HOW TO RECOGNIZE SYMPTOM

- Weight gain (by the time edema is clinically evident, a patient has typically gained 10 pounds)
- Swelling in distal extremities with presence of persistent indentation on skin following pressure (pitting edema)
- Fluid accumulation in dependent body parts
- Shortness of breath
- Jugular venous distension

CLINICAL INSIGHTS

Peripheral edema can be localized or generalized based on cause

Treatment is based on cause of edema:

- Discontinue medications that could be worsening edema (such as calcium channel blockers), if possible
- Mineralocorticoids increase sodium and water retention, hydrocortisone and prednisone have higher mineralocorticoid activity, consider alternate steroids in patients with edema (dexamethasone)
- Increasing doses of diuretics above the recommended max doses will not result in greater diuresis, rather it may cause more electrolyte disturbance

Edema (Peripheral)

NON-PHARMACOLOGICAL THERAPY

- Elevate feet above the heart while lying down unless contraindicated
- Evaluate current fluid intake; consider benefits / burden of potential reduction
- Lymphedema: lymphatic massages, wraps, or compression stockings

PHARMACOLOGICAL THERAPY

- Loop Diuretic Approximate Oral Equivalency: **Furosemide 40mg = Bumetanide 1mg = Torsemide 10-20mg = Ethacrynic Acid 50mg**
- Loop diuretics may require potassium replacement to prevent hypokalemia.
  - » Typical replacement ratio is 10meq K+: 20mg furosemide
  - » Some patients may require less, especially if receiving medications that increase potassium levels, such as ACE-inhibitors, angiotensin receptor blockers, or potassium sparing diuretics, or if they have a diagnosis of kidney disease.
- If dosing loop diuretics twice daily, the second dose should be given no later than early afternoon to prevent nocturia
- "Lasix Resistance" is lack of efficacy of furosemide despite adequate dosing and titration
  - » Potentially due to inter-individual genetic differences in furosemide absorption (bioavailablity can vary greatly)
  - » If dose seems ineffective, consider rotation to another loop diuretic. Use caution with equivalency table, may consider starting at initial dose of alternate diuretic and re-titrating
- Frequently evaluate diuretic regimen and cardiac medications for adjustment
- A target of weight loss of 1-2 pounds per day is recommended
- Patients with sulfa allergies will not necessarily have cross-reactivity with diuretics
- Ethacrynic acid (Edecrin) is the only commercially available loop diuretic that does not have sulfa cross-reactivity

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
LOOP DIURETICS				
Bumetanide (Bumex)	Initial (all forms): 0.5mg-1mg PO QD MDD (all forms): 10mg/day	Solution for injection: 0.25mg/ml Tablet: 0.5mg, 1mg, 2mg	• Taking with food decreases absorption • Injection route required during exacerbation of heart failure • May increase uric acid and worsen gout symptoms • May increase blood glucose	Y
Ethacrynic Acid (Edecrin)	Initial (PO): 50mg PO QD Initial (IV): 0.5-1mg/kg/dose MDD (PO): 400mg/day MDD (IV): Initial dose may be repeated Q8-12 hours	Solution for injection: 50mg Tablet: 25mg	• Drug of choice for patients with sulfa allergy • Avoid if CrCl < 10ml/min • IV form must be diluted with D5W or NS to 1mg/ml and infused over several minutes; should NOT be given SQ/IM • Expensive	Y
Furosemide (Lasix)	Initial (oral): 20-40mg QD Initial (IM,SQ,IV): 20-40mg QD MDD: Varies based on underlying disease Heart Failure: 4g/day Refractory HF: 8g/day Acute Renal Failure: 1-3g/day	Oral solution: 10mg/ml Solution for injection: 40mg/4ml Tablet: 20mg, 40mg, 80mg	• Onset: 30-60 min PO, 2-5min IV, and 30 min SQ • Injection route may be required during exacerbation of heart failure • Taking with food decreases absorption • Sublingual use of tablets may offer small improvements in absorption • May increase uric acid and worsen gout symptoms • May increase blood glucose	Y
Torsemide (Demadex)	Initial (all forms): 10-20mg QD MDD (all forms): 200mg/day	Solution for injection: 10mg/ml Tablet: 5mg , 10mg, 20mg, 100mg	• Useful if resistant to furosemide (Lasix)	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
THIAZIDE TYPE DIURETICS				
Chlorothiazide (Diuril)	Initial: 250-1000mg QD-BID MDD: 2,000mg/day	Oral suspension: 250mg/5ml Solution for injection: 500mg Tablet: 250mg, 500mg	• Ineffective if CrCl < 30ml/min; Avoid use if CrCl < 10ml/min • Use caution in inpatients with hypercalcemia in that it can decrease renal calcium excretion • Can be given IV (NOT IM or SQ)	Y
Chlorthalidone (Thalitone)	Initial: 50-100mg QD MDD: 200mg/day	Tablet: 25mg, 50mg, 100mg	• Avoid use if CrCl < 10ml/min • Use caution in patients with hypercalcemia in that it can decrease renal calcium excretion	Y
Hydrochlorothiazide (Microzide)	Initial: 25-100mg PO divided QD-BID MDD: 200mg/day	Capsule: 12.5mg Tablet: 12.5mg, 25mg, 50mg	• Ineffective if CrCl < 30ml/min; Avoid use if CrCl < 10ml/min • May increase uric acid and worsen gout symptoms • May increase blood glucose	Y
Indapamide (Lozide)	Initial: 2.5mg QD MDD: 5mg/day	Tablet: 1.25mg, 2.5mg	• There is limited therapeutic benefit with doses >5mg and can be associated with increased electrolyte imbalance • Take with food/milk to decrease GI irritation	Y
Metolazone (Zaroxolyn)	Initial: 2.5-5mg PO QD MDD: 20mg/day	Tablet: 2.5mg, 5mg, 10mg	• Preferred thiazide diuretic for patients with renal impairment • When using in conjunction with a loop diuretic for edema secondary to heart failure, initial dose should be 2.5mg • Often given 30min prior to loop diuretic for improved diuresis	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
POTASSIUM SPARING DIURETIC				
Amiloride (Midamor)	Initial: 10mg BID MDD 60mg/day	Tablet: 5mg	• Avoid if CrCl < 10ml/min • Off label use for ascites • Take with food/meals to decrease GI irritation	Y
Eplerenone (Inspra)	Initial: 25mg QD MDD: Not established for this indication.	Tablet: 25mg, 50mg	• Consider use if gynecomastia occurs with spironolactone • Avoid if CrCl < 30ml/min • Doses greater than 50mg typically not seen	Y
Spironolactone (Aldactone)	Initial: 25mg PO QD MDD: 200mg/day	Tablet: 25mg, 50mg, 100mg	• Preferred potassium sparing diuretic • Side effects: gynecomastia, impotence • Avoid use if CrCl < 10ml/min • Take with food to decrease GI irritation and increase absorption • For treatment of ascites: Use ratio of 100mg spironolactone/ 40mg furosemide to avoid electrolyte abnormality	Y
Triamterene (Dyrenium)	Initial: 100-300mg QD in divided doses MDD: 300mg/day	Tablet: 50mg, 100mg	• Avoid if CrCl < 50ml/min • May increase uric acid and worsen gout symptoms • May increase blood glucose	Y
CARBONIC ANHYDRASE (CA) INHIBITORS				
Acetazolamide (Diamox)	Initial: 250mg – 375mg QD MDD: Not established for this indication	Capsule (ER)*: 500mg Solution for injection: 500mg Tablet: 125mg, 250mg	• Uses include: adjunct diuretic therapy for CHF, drug induced edema • Avoid use if CrCl < 10ml/min • Side effects: metabolic acidosis, alteration of blood glucose	Y/N*

References

- Beattie, J. et al. Subcutaneous furosemide in advanced heart failure: has clinical practice run ahead of the evidence base? BMJ Supportive & Palliative Care, 2012, Vol. 2, No.1.
- Cho S, Atwood JE. Peripheral Edema. Am J Med. 2002 Nov;113(7):580-6.
- Crandall ED, Staub NC, Goldberg HS, Effros RM. Recent developments in pulmonary edema. Ann Intern Med 1983; 99:808-816
- Ely JW, Osheroff JA, Chambliss L, et al. Approach to Leg Edema of Unclear Etiology. J Am Board Fam Med 2006;19:148–60.
- Farless, L. et al. Intermittent subcutaneous furosemide: parenteral diuretic rescue for hospice patients with congestive heart failure resistant to oral diuretic, American Journal of Hospice and Palliative Medicine, 2012, 300(8)791-2.
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 93.
- Goenaga, M. et al. Subcutaneous furosemide, The Annals of Pharmacotherapy, 2004, Vol. 38.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 972-981,1257-66.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- O'Brien JG, Chennubhotla SA, Chennubhotla RV. Treatment of Edema. Am Fam Physician 2005;71(11):2111- 2118.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 173.
- Sterns RH, Emmett M, Forman JP, et al. General principles of the treatment of edema in adults, UpToDate.com, 2015. Accessed online July 2015.
- Verma, A. et al. Diuretic effects of subcutaneous furosemide in human volunteers: a randomized pilot study, Annals of Pharmacotherapy, 2004, Vol. 38, pp. 544-9

Fever

DEFINITION

An increase in body temperature above the normal range, generally considered to be between 97.7 and 99.9 degrees (oral) Fahrenheit.

CAUSES

- Infection (> 50% of cases)
- Cancer (most commonly Hodgkin's disease, kidney cancer, leukemia, lymphoma, colon cancer, sarcoma and adrenal carcinoma)
- Medications: allopurinol, captopril, cimetidine, heparin, isoniazid, meperidine, nifedipine, phenytoin, diuretics, barbiturates, antihistamines, ephedra containing supplements, volatile anesthetic gases, antipsychotics, medications that increase serotonergic activity, anticholinergic medications
- Specific types of drug induced fever exist:
  - » Malignant hyperthermia – exposure to volatile anesthetic (ex: halothane, isoflurane)
  - » Neuroleptic malignant syndrome – exposure to antipsychotics
  - » Serotonin syndrome – exposure to serotonergic medications
  - » Anticholinergic toxicity – exposure to anticholinergics
- Blood transfusion
- Certain immunizations
- Immunocompromised
- Hormonal dysfunction
- Inflammatory conditions, such as rheumatoid arthritis
- Environmental temperature / heat stroke
- Radiation-induced
- Thromboembolic processes such as DVT or PE
- Cerebrovascular Accident (CVA)
- Cirrhosis
- Temporal arteritis
- Collagen vascular diseases such as systemic lupus erythematosus (SLE)

HOW TO RECOGNIZE SYMPTOM

- Elevated body temperature
- Fever due to infection:
  - » Chills, night sweats, muscle pain, weight loss with intact appetite
- Fever due to inflammatory causes:
  - » Joint pain, muscle pain, fatigue
- Fever due to neoplasm:
  - » Fatigue, night sweats, weight loss with loss of appetite
- Rigors
- Headache
- Mental status change

CLINICAL INSIGHTS

- Fever is a frequent end-of-life symptom arising from myriad causes
- Rectal temperatures tend to be higher than oral or axial temperatures
- If treatment of fever is required, determine cause of fever whenever possible.
- Non-pharmacological may be considered for fever of any type or origin:
  - » Provide fluid replacement with clear liquids
  - » Encourage nutritional intake, as indicated
  - » Consider bathing patient with lukewarm water (do not use cold water or alcohol)
- If the fever is due to infection, a decision to treat with antibiotics should be based on numerous factors such as severity of symptoms, risk-benefit ratio, goals of care, and expected symptomatic benefit
- Concomitant administration of antipyretics (including steroids) can mask antibiotic treatment failure (fever will be reduced with no effect on the infection)
- While any NSAID can be effective for decreasing fever, ibuprofen and naproxen are the most commonly used in the hospice setting and are cost-effective
- For an unremitting fever, alternating acetaminophen and an NSAID can be useful

- Neutropenic patients are more prone to bleeding; avoid rectal administration of medications to prevent rectal bleeding
- For unexplained fever, review the patients medication profile and symptoms to assess the potential for medication induced syndromes, including serotonin syndrome, neuroleptic malignant syndrome, or anticholinergic syndrome (**Table 1**)

TABLE 1 – COMPARISON OF DRUG-INDUCED FEVER SYNDROMES

	SEROTONIN SYNDROME	ANTICHOLINERGIC TOXICITY	NEUROLEPTIC MALIGNANT SYNDROME (NMS)
Induced By	Serotonergic drugs	Anticholinergic drugs	Dopamine blocking drugs (esp. antipsychotics)
Time To Onset Needed	< 12 hours	< 12 hours	1-3 days
Typical Fever Severity	> 41.1C	≤ 38.8C	> 41.1C
Pupils	Mydriasis	Mydriasis	Normal
Mucosa	Sialorrhea	Dry	Sialorrhea
Skin	Diaphoresis	Red; hot and dry to touch	Pallor with diaphoresis
Neuromuscular Tone	Increased; esp. in legs	Normal	Full body “lead pipe” rigidity
Mental Status	Agitation, coma	Agitated delirium	Stupor, alert mutism, coma
Pharmacological Treatment After Discontinuing Offending Agent(S)	Short-acting parenteral beta-blockers for autonomic instability Cyproheptadine to reverse serotonin Benzodiazepines for sedation NO role for APAP	Benzodiazepines for agitation / delirium +/- activated charcoal NO role for APAP	Benzodiazepines if agitation present Dantrolene for fever Bromocriptine or amantadine to overcome dopamine block Possible role of APAP

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Acetaminophen (Tylenol)	Initial: 325-650mg PO/PR Q 4-6 hours PRN MDD: 3,000-4,000mg/day	Oral solution: 160/5ml Other formulations exist Suppository: 650mg Tablet: 325mg, 500mg Tablet (ER)*: 650mg	• Monitor for additional sources of acetaminophen that may contribute to overdose / exceeding max daily dose • Consider risks versus benefits in patients with hepatic insufficiency although patients with cirrhosis typically will tolerate therapeutic doses	Y/N*
Aspirin (Bayer, Ecotrin, others)	Initial (PO): 325-650mg Q 4-6 hours PRN Initial (PR): 300-600mg Q 4-6 hours MDD: 4,000mg/day	Chewable tablet: 81mg Suppository: 300mg, 600mg Tablet: 81mg , 325mg, 500mg Tablet (EC)*: 81mg, 325mg, 500mg, 650mg	• Use with caution in patients with decreased platelet activity • Only NSAID commercially available in suppository dosage form • Compared to other NSAIDs, moderate GI risk; low cardiovascular risk	Y/N*
Ibuprofen (Advil, Motrin)	Initial: 400-800mg Q 6-8 hours PRN MDD: 3,200mg/day	Tablet: 100mg, 200mg, 400mg, 600mg, 800mg Capsule*: 200mg Oral suspension: 100mg/5ml Other formulations exist	• Typically avoided in patients with cardiac or renal disease; risks versus benefits should be assessed on an individual basis • Can be compounded into a suppository dosage form • Compared to other NSAIDs, low GI risk; moderate to high cardiovascular risk	Y/N*
Naproxen (Aleve, Naprosyn)	Initial: 220mg PO Q 8-12 hours PRN MDD: 1,000mg/day	Tablet (naproxen sodium): 220mg (OTC), 275mg, 550mg Tablet: 250mg, 375mg, 500mg Tablet (EC)*: 375mg, 500mg Tablet (ER)*: 375mg, 500mg, 750mg	• Naproxen sodium 220mg = 200mg naproxen • Compared to other NSAIDs, moderate to high GI risk; low cardiovascular risk	Y/N*

References

- Bor, D. et al. Approach to the adult with fever of unknown origin, UpToDate.com – current through Oct. 2015.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 736-42.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 179-181.
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 99.
- Lexi-comp 5-minute clinical consult: fever of unknown origin
- Lexi-comp charts and special topics: serotonin syndrome
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Porat, R. et al. Pathophysiology and treatment of fever in adults, UpToDate.com – current through Oct. 2015.Verma, A. et al. Diuretic effects of subcutaneous furosemide in human volunteers: a randomized pilot study, Annals of Pharmacotherapy, 2004, Vol. 38, pp. 544-9

Headache

DEFINITION

A headache is neurologic event that causes pain in one or both sides of the head, including scalp, face, and interior of the head.[1-3]

CAUSES

- Primary headaches lack an identifiable cause.
- Secondary headaches have several potential underlying causes (**Table 1**), including drug side effects (**Table 2**).

HOW TO RECOGNIZE SYMPTOM

- When able to do so, patients will generally self-report headaches. Clinicians should inquire about characteristics, including response to previous treatment attempts, to aid in classification and treatment.
- In non-verbal patients, vomiting, grimacing, tense/distressed appearance, behavioral changes may indicate headache.

CLINICAL INSIGHTS

- Headache incidence generally decreases with age, although older adults are at higher risk for secondary headaches.[2, 4]
- Non-pharmacologic treatment options (**Table 3**) should be optimized to prevent polypharmacy and overuse of medications.[2, 5, 6]
- Description, location, severity, onset, triggers, associated features, and duration are used to classify primary headaches (**Table 4**).
- Tension-type headache (TTH), also called "stress headache", is the most common new-onset headache type in geriatric patients[7]
- The "POUND" mnemonic is used to aid migraine diagnosis, especially if patient presents with 4 or more of the following:
  - » **P**ulsatile quality
  - » **O**ne-day duration (4-72 hours)
  - » **U**nilateral location
  - » **N**ausea / vomiting
  - » **D**isabling intensity
- Migraine aura is a reversible set of neurologic symptoms and sensory or physical occurrences that can precede or accompany a migraine.[8, 9]
  - » Aura typically evolves over 5 minutes and lasts less than 60 minutes.[9]
  - » Headache usually occurs within 60 minutes of the end of aura.[9]
  - » Visual changes are the most common form of aura and may include seeing spots, zigzags, flashes of light, and full or partial loss of sight.
  - » Scintillating scotoma, also called a visual migraine, is a common visual aura preceding migraine that starts as a blind spot of flickering light near the center of the visual field that gradually expands outward.
  - » Sensory changes may involve tingling or numbness on one side of the face, body, or tongue.
  - » Patients may have difficulty speaking or finding the right words to express an idea.
- As a group, trigeminal autonomic cephalalgias (TACs) are rare; the most common TAC is cluster headache.
  - » A unique characteristic of some TACs is their responsiveness to indomethacin treatment.
- Drug treatment should consider the following:
  - » Suspected type of headache (**Table 3**)
  - » Comorbidities
  - » Potential consequences of polypharmacy (eg, drug interactions, therapeutic competition, pill burden)
  - » Possibility of medication overuse
  - » Altered pharmacokinetics
    - ° Renal or hepatic impairment can affect drug clearance / metabolism
    - ° Oral absorption can be delayed during migraine attacks[6]
  - » Adverse effects
- NSAIDs are first-line therapy for mild to moderate migraine and tension-type headaches.[5, 6, 10]
  - » Use is cautioned in elderly patients due to increased risk of cardiovascular and gastrointestinal adverse effects.
  - » Addition of caffeine tablets has been shown to be more efficacious than single agents[5]

- Both NSAIDs and triptans cause vasoconstriction and can exacerbate hypertension, a potential cause of headaches.[6, 11, 12]
- Ergotamines are rarely used due to the availability of more effective and better-tolerated drugs.
- Secondary headaches have characteristic descriptions and features and treatment is individualized based on underlying cause(s) (**Table 1**).
- Medication overuse headache can occur with excessive drug treatment for acute episodes, but can be prevented by limiting treatments to not more than:[13]
  - » 9 days per month for triptans, erogtamines or combination analgesics
  - » 14 days per month for NSAIDs
  - » 3 days per month for butalbital-containing treatments

TABLE 1 – CAUSES OF SECONDARY HEADACHES[1–3, 7, 9, 11]

CAUSE	EXAMPLES
Substance related	Medication side effects Medication overuse headache Medication or substance withdrawal (eg., caffeine)
Ocular/Orbital	Acute angle closure glaucoma
Traumatic	Acute or chronic subdural hematoma
Vascular	Giant cell arteritis (more prevalent in geriatric patients) Stroke Cortical vein and venous sinus thrombosis Cardiac cephalalgia (associated with myocardial ischemia) Cervical artery dissection Idiopathic intracranial hypertension
Brain mass/ lesion	Primary and metastatic brain tumors
Disorder of homeostasis	Obstructive sleep apnea Hypothyroidism Acute severe hypertension
Infection	Post-herpetic neuralgia Meningitis Brain abscess
Bone and structural	Skull metastases Acute or subacute neck pain with Horner syndrome and/or neurologic deficit

TABLE 2 – MEDICATIONS THAT CAN CAUSE HEADACHE AS AN ADVERSE EFFECT[7]

MEDICATION TYPE	EXAMPLES
Circulatory drugs	Calcium channel blockers Dipyridamole Hydralazine Nitrates Phosphodiesterase inhibitors Sympathomimetic agents
Antidepressants	Monoamine Oxidase Inhibitors (MAOIs) Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) Selective Serotonin Reuptake Inhibitors (SSRIs)
Antibiotics	Tetracyclines Trimethoprim
Methylxanthines	Theophylline Caffeine
Anti-Parkinson drugs	Amantadine Levodopa
Other	Phenothiazines Proton Pump Inhibitors (PPIs) Corticosteroids Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Estrogen Tamoxifen Antihistamines

TABLE 3 – TREATMENT OF PRIMARY HEADACHES[2, 4, 6–8, 10–15]

TENSION-TYPE HEADACHE	MIGRAINE	CLUSTER HEADACHE
Non-pharmacologic therapy		
Relaxation, massage, ice, heat, trigger point injections, physical therapy	Rest, relaxation, massage, heat, ice	None
Pharmacologic therapy		
NSAIDs, APAP, butalbital-containing medications	ASA, NSAIDs, APAP, APAP/ASA/caffeine, triptans, antiemetics, ergotamines	Oxygen, triptans

TABLE 4 – PRIMARY HEADACHE CHARACTERISTICS[2, 4, 6 – 8, 10 – 15]

TYPE	TENSION-TYPE HEADACHE	MIGRAINE	CLUSTER HEADACHE
Descriptors	Non-throbbing Dull Pressure "like a tight cap" "heavy weight on head or shoulders"	Throbbing Pounding Pulsating	Excruciating pain
Location	Bilateral, affecting head and neck	Usually unilateral, occurring in frontotemporal regional (but may occur anywhere in face or head)	Always unilateral; temporal, centered around one eye
Severity	Mild to moderate	Moderate to severe; interferes with normal functioning	Severe
Onset	Within 30 minutes	30 minutes to 1 hour	< 1 minute
Duration	30 minutes to 7 days	4-72 hours	15-180 minutes
Triggers	• Anxiety • Insomnia • Medication overuse • Stress	• Hunger • Medication overuse • Food and food additives • Alcohol • Odor • Sleep disturbances • Stress • Visual stimuli • Hormone fluctuations	• Alcohol • Histamine • Nitroglycerin
Associated features	Infrequent or chronic May be precipitated or aggravated by migraine Muscle tenderness in head, neck, or shoulders Pain not affected by routine physical activity	May occur with our without aura Usually accompanied by GI symptoms (ie, nausea/vomiting) Aggravated by routine physical activity Premonitory/prodromal symptoms may begin hours or days before headache Postdromal symptoms may follow HA and persist for up to 48 hours	Cluster of attacks during several weeks separated by remission periods lasting anywhere from 14 days to several months Cranial autonomic signs/ symptoms present ipsilateral (on the same side of the body) to headache: » Red, teary eyes » Drooping eyelids » Eyelid edema » Constricted pupils » Nasal congestion / rhinorrhea » Forehead / facial sweating Possible restlessness / agitation

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
TRIPTANS[2, 13, 14, 16, 17]				
Almotriptan (Axert)	Initial: 6.25-12.5mg PO at onset of headache, repeated in 2 hours if needed MDD: 25mg/day (12.5mg/day if combined with potent CYP3A4 inhibitors)	Tablet: 6.25mg, 12.5mg	**Triptans** • First-line therapy for severe migraine • SQ and nasal formulations have faster onset than oral formulations • Limit to ≤9 days to prevent medication overuse headache • May cause somnolence and fatigue • Many patients report "triptan sensations," including tightness, pressure, heaviness, or pain in the chest, neck, or throat • May cause serotonin syndrome when combined with serotonin reuptake inhibitors or certain opioid analgesics • Contraindicated in patients with ischemic heart disease, cerebrovascular disease, and uncontrolled hypertension • Do not use within 2 weeks of a MAOI **Eletriptan** • Avoid use with potent CYP3A4 inhibitors within 72 hours **Frovatriptan** • Longest half-life (25 hours) but slowest onset of action • Least effective triptan **Rizatriptan** • Dose adjustment with concomitant propranolol therapy: 5mg/dose (MDD: 15mg/day) **Sumatriptan** • SQ formulation most effective • Nasal spray can be given for cluster HA in single nostril contralateral to side of headache • Contraindicated if severe hepatic impairment • Highest incidence of adverse effects among triptans • Available in combination with naproxen **Zolmitriptan & Sumatriptan** • Faster onset than other triptans **Almostriptan, Naratriptan, Sumatriptan** • Require hepatic and renal dose adjustment	Y
Eletriptan (Relpax)	Initial: 20-40mg PO at onset of headache, repeated in 2 hours if needed MDD: 80mg/day	Tablet: 20mg, 40mg		Y
Frovatriptan (Frova)	Initial: 2.5mg PO at onset of headache, repeated in 2 hours if needed MDD: 7.5mg/day	Tablet: 2.5mg		Y
Naratriptan (Amerge)	Initial: 1-2.5mg PO at onset of headache, repeated in 4 hours if needed MDD: 5mg/day	Tablet: 1mg, 2.5mg		Y
Rizatriptan (Maxalt, Maxalt-MLT)	Initial: 5-10mg PO at onset of headache, repeated in 2 hours if needed MDD: 30mg/day	Oral Disintegrating Tablet (ODT)*: 5mg, 10mg Tablet: 5mg, 10mg		Y/N*
Sumatriptan (Imitrex, Onzetra, Tosymra)	Initial (PO): 25-100mg at onset of headache, repeated in 2 hours if needed (mild-moderate hepatic impairment: max 50mg/ dose) Initial (intranasal): 5-20mg in single nostril at onset of headache, repeated in 2 hours if needed Initial (SQ): 6mg at onset of headache, repeated after ≥1 hour if needed MDD (PO): 200mg/day MDD (intranasal): 30mg/day (nasal spray), 40mg/day (nasal solution) MDD (SQ): 12mg/day	Nasal Solution: 5mg, 20mg Nasal Spray: 10mg Solution for injection: 3mg/0.5ml, 4mg/0.5ml, 6mg/0.5ml Tablet: 25mg, 50mg, 100mg		Y
Zolmitriptan (Zomig, Zomig ZMT)	Initial (PO): 1.25-2.5mg at onset of headache, repeated in 2 hours if needed Initial (intranasal): 2.5mg at onset of headache, repeated in 2 hours if needed MDD: 10mg/day	Nasal Spray: 2.5mg, 5mg Oral Disintegrating Tablet (ODT)*: 2.5mg, 5mg Tablet: 2.5mg, 5mg		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) [2, 5, 6, 13, 14, 16 – 19]				
Aspirin (Ecotrin, Bayer)	Initial: 500-1,000mg PO/ PR Q4-6 hours PRN MDD: 4,000mg/day	Capsule (EC)*: 325mg Chewable tablet: 81mg Suppository: 300mg, 600mg Tablet: 81mg, 325mg, 500mg Tablet (EC)*: 81mg, 325mg, 500mg, 650mg	**NSAIDs** • First-line therapy for mild to moderate migraine and TTH • Restrict use to ≤15 consecutive days to prevent medication overuse headache • May cause GI upset; take with food or milk • Increased risk of cardiovascular events and GI bleeding • Caution if renal or hepatic impairment • Delayed-release, enteric-coated, and extended-release dosage forms are not recommended for acute treatment due to slow absorption **Ibuprofen** • Most extensively studied NSAID for treating TTH **Naproxen sodium** • Long-acting NSAID • 220mg naproxen sodium = 200mg naproxen base • Naproxen sodium preferred over naproxen base for acute pain due to more rapid absorption and onset **Diclofenac potassium** • Diclofenac potassium preferred over diclofenac sodium for acute pain due to faster onset • Increased risk of vascular events (eg., stroke, non-fatal MI) when doses exceed 100mg/day • Highest risk of liver toxicity compared to other NSAIDs • Lower doses (12.5-25mg) may be effective for episodic TTH **Indomethacin** • First-line for certain types of TACs and headaches provoked by exercise or cough • May cause dose-related headache; recommend using the lowest-effective dose and consider gradual dose reductions every 3 to 6 months • Expensive	Y/N*
Diclofenac potassium (Cataflam, Cambia, Zipsor)	Initial (TTH): 12.5-25mg PO at onset of headache Initial (migraine): 50-100mg PO at onset of headache; repeat with 50mg in 8 hours if needed MDD: 100-150mg/day	Capsule: 25mg Powder: 50mg Tablet: 50mg		Y
Ibuprofen (Advil, Motrin)	Initial: 400mg-800mg PO Q4-8 hours PRN MDD: 3,200mg/day	Capsule: 200mg Chewable tablet: 50mg, 100mg Oral suspension: 100mg/5ml, 50mg/1.25ml Tablet: 200mg, 400mg, 600mg, 800mg		Y
Indomethacin (Indocin)	Initial (IR): 25mg PO TID x 3 days, then increase to 50mg TID MDD: not established for this indication; 225mg/day cited as threshold for determining responsiveness, but doses up to 500mg/day have been reported	Capsule: 20mg, 25mg, 50mg Capsule (ER)*: 75mg Oral suspension: 25mg/5ml Suppository: 50mg		Y/N*
Naproxen sodium (Aleve)	Initial (IR): 825mg PO at onset of headache; an additional 275-550mg may be given if needed MDD: 1,375mg/day	Capsule: 220mg Tablet: 220mg, 275mg, 550mg Tablet (ER)*: 375mg, 500mg, 750mg		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER [16]				
Acetaminophen (Tylenol)	Initial (IR): 325mg-1,000mg PO/PR at onset of headache, repeated Q4-6 hours if needed Initial (ER): 650mg-1,300mg PO Q8 hours as needed MDD: 3,000-4,000mg/day	Chewable tablet: 80mg, 160mg Oral solution: 160mg/5ml, 500mg/15ml Suppository: 80mg, 120mg, 325mg, 650mg Tablet: 325mg, 500mg Tablet (ER)*: 650mg	• First-line therapy for mild to moderate migraine and TTH • Monitor combined use of acetaminophen from all sources so not to exceed daily maximum of 3-4 grams/day • Consider reduced daily acetaminophen dose (ie, MDD 2-3 grams/day) if severe hepatic impairment	Y/N*
Acetaminophen/ Aspirin/ Caffeine (Excedrin Migraine)	Initial: 2 tablets PO at onset of headache MDD: 8 tablets/day	Tablet: 250/250/65mg, 130/260/16.25mg, 194/227/33mg		Y
BUTALBITAL COMBINATION PRODUCTS [13, 16]				
Butalbital/ Aspirin/ Caffeine (Fiorinal)	Initial: 1-2 capsules PO Q4 hours PRN MDD: 6 capsules or tablets/day	Capsule: 50/325/40mg Tablet: 50/325/40mg	• Effective for treating TTH • Not recommended for routine use due to high potential to cause medication overuse headache • Limit use to ≤3 days/month to prevent medication overuse headache • Associated with analgesic rebound, intoxication, tolerance, and dependence • Monitor combined use of acetaminophen from all sources so not to exceed daily maximum of 3-4 grams/day • Total daily dose of butalbital should not exceed 300mg/day	Y
Butalbital/ Acetaminophen/ Caffeine (Fioricet, Esgic)	Initial: 1-2 tablets PO Q4 hours PRN MDD: 6 capsules or tablets/day	Capsule: 50/300/40mg, 50/325/40mg Tablet: 50/325/40mg		Y
Butalbital/ Acetaminophen/ Caffeine/ Codeine (Fioricet with Codeine)	Initial: 1-2 capsules PO Q4 hours PRN MDD: 6 capsules/day	Capsule: 50/300/40/30mg, 50/325/40/30mg		Y
Butalbital/ Aspirin/ Caffeine/ Codeine (Fiorinal with Codeine)	Initial: 1-2 capsules PO Q4 hours PRN MDD: 6 capsules/day	Capsule: 50/325/40/30mg		Y

References

1. Porter, R; Kaplan, J; Homeier, B. Merck Manual of Patient Symptoms: Headache Chapter. 2008. Merck & Co. Inc. 264-271.
2. Starling, A. Diagnosis and Management of Headache in Older Adults. Mayo Clinic: Symposium on Neurosciences. 2018; 93(2):252-262.
3. Kaplan J; Porter R; et. al. Approach to the Patient with Headache. Merck Manual Professional Version. Whitehouse Station, NJ. Merck Sharp & Dohme Corp. 2018. STAT!Ref Online Electronic Medical Library.
4. Hershey L; Bednarczyk E. Treatment of Headache in the Elderly. Current Treatment Options in Neurology. February 2013; 15(1):56-62.
5. Taylor F; Swanson J; Dashe J. UpToDate: Tension-type headache in adults: acute treatment. January 24, 2017. Accessed November 19, 2018.
6. Minor D; T Harrell. Headache Disorders. In: DiPiro J; Talbert R; et. al. Pharmacotherapy: A Pathophysiologic Approach, 10e. New York, NY: McGraw-Hill Education. 2017.
7. Robbins M; Lipton R. Management of Headache in the Elderly. Drugs and Aging. May 2012; 27(5):377-398.
8. Bajwa Z; Wootton J. UptoDate: Patient education: headache causes and diagnosis in adults (beyond the basics). July 21, 2017. Accessed November 19, 2018.
9. Topper D. Headache Toolbox: Aura with Headache. The Journal of Head and Face Pain. American Headache Society. 2014; 1115-1116.
10. Bendtsen L; Evers S; Linde M; Mitsikostas D; et al. EFNS guideline on the treatment of tension-type headache -- report of an EFNS task force. European Journal of Neurology. 2010; 17(11).
11. Chai, E; Meier, D; Morris, J; Goldhirsch, S. Geriatric Palliative Care: a practical guide for clinicians. 2014. Oxford University Press. 209–212.
12. Bajwa Z; Wootton J; Wippol F; et al. UpToDate: Evaluation of headache in adults. October 26, 2018. Accessed November 19, 2018.
13. Bajwa Z; Wooton J. UpToDate. Patient education: headache treatment in adults (Beyond the Basics). July 21, 2017. Accessed November 19th, 2018
14. Melzack R; Wall P. Handbook of Pain Management. Headache chapter. 2003. Elsevier Limited. 217-245.
15. Berk T; Ashina S; et.al. Diagnosis and Treatment of Primary Headache Disorders in Older Adults. Journal of the American Geriatric Society. 2018.
16. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer UpToDate, Inc.; 2020.
17. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018; 38(1):1–211.
18. AHFS Drug Information. AHFS Clinical Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, Inc. Updated March 2020.
19. Bordini EC, Bordini CA, Woldeamanuel YW, Rapoport AM. Indomethacin Responsive Headaches: Exhaustive Systematic Review With Pooled Analysis and Critical Appraisal of 81 Published Clinical Studies. Headache: The Journal of Head and Face Pain. 2016;56(2):422-435.

Hemorrhoids

DEFINITION

A clump of dilated veins or group of veins under the skin in the walls of the anus or in the lower rectum. They are classified as external or internal. Hemorrhoids are also known as piles.

CAUSES

- Hemorrhoids are common in U.S. adults, with the highest rates for those between ages 45 and 65 years.
- Main causes for hemorrhoids include factors that increase intra-abdominal pressure to contribute to dilatation, engorgement, and prolapse of hemorrhoidal vascular tissue, including:
  - » Prolonged straining on the toilet
  - » Chronic constipation or diarrhea
  - » Pregnancy
  - » Ascites
  - » Obesity
  - » Low fiber/high processed food diet
  - » Changes in medical condition, fluid intake or fiber intake associated with EOL disease

HOW TO RECOGNIZE SYMPTOM

- Most common symptoms of hemorrhoids include:
  - » Anal discharge
  - » Itching
  - » Prolapse
    - ° Hemorrhoids protrude outside the anus
  - » Bleeding
  - » Pain
- Two types of hemorrhoids
  - » Internal hemorrhoids
    - ° Anal discharge
    - ° Itching
    - ° Prolapse
    - ° Painless rectal bleeding
      - › Blood on the toilet paper or bleeding associated with bowel movements
  - » External hemorrhoids
    - ° Anal discharge
    - ° Itching
    - ° Anal discomfort
      - › Caused by engorgement
    - ° Acute pain with or without bleeding
      - › Caused by thrombosis

CLINICAL INSIGHTS

- Drug therapy consists of topically applied vasoconstrictors, steroids, and anesthetics
- Increase intake of fiber/fiber supplements and fluids as tolerated
  - ° Examples include psyllium or methylcellulose
  - ° Doses targeting 20 – 30g/day
  - » It is important to educate patients/caregivers on the importance of diet, as tolerated
- Use stool softeners (as tolerated) to decrease pain, bleeding, prolapse and itching
- Sitting on a cushion or hemorrhoidal ring, rather than a hard surface, can help reduce swelling of existing hemorrhoids
- General treatment includes;
  - » Local application of ice packs, cold compresses, witch hazel wipes, zinc oxide to prevent rash associated with challenges in cleaning the perianal area
- Protruding hemorrhoids can collect small amounts of mucus and microscopic stool particles that may cause an irritation called pruritis ani. This can cause severe itching which results in additional wiping of the area which can exacerbate discomfort or bleeding.
- When the urge to defecate emerges counsel the patient to go to the bathroom immediately. Waiting for a more convenient time may cause buildup of stool, leading to increased pressure and pain
- Treatment of symptoms include:
  - » For itching or irritation
    - ° Analgesic creams
    - ° Hydrocortisone suppositories
    - ° Witch hazel wipes
    - ° Warm sitz baths
      - › 3-6 times/day
  - » For bleeding
    - ° Dietary modification
    - ° Persistent bleeding: rubber band procedure

  - For thrombosis (usually with pain)
    - Dietary modification
    - Agents to treat pain
  - For prolapse
    - Rubber band ligation
    - Surgery

- Surgical options are indicated for patients whose symptoms cannot be managed by traditional treatments, however risk/benefit may not be warranted for EOL patients
  - Excisional hemorrhoidectomy
  - Stapled hemorrhoidopexy
  - Rubber band ligation
  - Infrared coagulation
  - Injection sclerotherapy

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Dibucaine (Nupercainal Rectal)	Apply to affected external anal area up to 3 or 4 times daily	1% ointment (28g) OTC	• For pain and itching • Apply to clean dry area	-
Hydrocortisone (Anusol-HC, Proctosol HC, Sarnol-HC)	Hydrocortisone (1% cream, 1% gel, 1% lotion, 1% ointment): Apply to affected area 2 to 4 times daily One suppository (25 or 30mg) twice daily for 2 weeks	1% cream, gel, lotion, ointment (15-80g) OTC Suppository 25-30mg (12) OTC	• For itching or inflammation • Apply a thin film to clean, dry skin and rub in gently • Shake lotion well before use	-
Lidocaine (LMX 5)	Apply to affected area up to 6 times daily	5% Cream (15-30g) OTC	• For pain and itching • Apply to clean dry area • May cause redness, edema, or skin discoloration	-
Phenylephrine (Preparation H Rectal)	Apply ointment up to 4 times/day Insert 1 suppository rectally up to 4 times/ day	0.25-14-74.9% ointment (28g) OTC 0.25-88.44% suppositories (12) OTC	• Apply to clean dry area • For swelling, burning, pain, and itching	-
Pramoxine (ceraVe itch, Proctofoam, Tronolane, etc.)	Apply to affected area up to 5 times daily	1% cream (340g) OTC, 1% ointment, 1% aerosol foam	• For pain and itching • Many products available	-
Witch Hazel (Preparation H Totables)	Apply to anorectal area as needed up to 6 times daily or after each bowel movement	50% External pads (10-100) OTC 86% Solution (473ml) OTC	• For discomfort from hemorrhoids • Available as a solution or pre-moistened wipes	-

References

- http://www.aafp.org/afp/2011/0715/p204.html
- https://www-uptodate-com.proxy.lib.uiowa.edu/contents/treatment-of-hemorrhoids?source=search_result&search=hemorrhoids&selectedTitle=1~150
- https://www.guideline.gov/expert/expert-commentary/37828/management-of-hemorrhoids-mainstay-of-treatment-remains-diet-modification-and-officebased-procedures
- https://gi.org/wp-content/uploads/2014/07/ACG_Guideline_Benign_Anorectal_Disorders_August_2014.pdf

Hiccough

DEFINITION

A repeated, involuntary contraction of the diaphragm followed by closure of the vocal cords causing the "hic" sound. Chronic hiccups can last days to weeks and be troublesome to the patient. Hiccoughs are classified as acute if lasting up to 48 hours, persistent if lasting more than 48 hours, and intractable if more than a month.

CAUSES

- Gastric Irritation:
  - Overeating/ rapid gastric distention
  - Eating or drinking too quickly
  - Carbonated beverages
  - Spicy foods
  - Sudden change in ingested food temperature (hot or cold food/drinks)
  - Alcohol
- Hyperventilation
- Swallowing air
- Medical Conditions:
  - CNS disorders
    - Stroke, inflammation, trauma, seizure, aneurysm, lesions, Multiple Sclerosis
  - Gastrointestinal Disorders
    - Cholecystitis, GERD, pancreatitis, bowel obstruction, ulcer, gastritis, gastric dysmotility
  - Thorax
    - Pericarditis, esophagitis, laryngitis, pharyngitis, nerve irritation of neck or diaphragm, goiter
  - Cancer/Tumor
  - Infection (especially oral candidiasis, pneumonia)
  - Psychogenic
    - Fear, laughter, shock, grief, schizophrenia
  - Metabolic disorders
    - Uremia, hypocalcemia, hyponatremia, hypokalemia, hyperglycemia
- Medications
  - Corticosteroids, benzodiazepines, opioids, barbiturates, anti-dopaminergic, chemotherapy, azithromycin, methyldopa
- Tobacco use and alcohol intoxication

HOW TO RECOGNIZE SYMPTOM

- Involuntary contraction of one/both sides of the diaphragm
- A "hiccup" sound is produced at the end of the contraction due to abrupt closure of the glottis
- Hiccup spasms can often be seen by patient abdomen

CLINICAL INSIGHTS

- Higher incidence in men than women
- Can lead to decreased oral intake which can lead to weight loss, dehydration, malnutrition, exhaustion, fatigue

APPROACHING THERAPY

- There is no consensus statement on treatment of hiccoughs
- Therapy should be dependent on the cause. Assess patient's potential causes to help guide therapy
- Individuals respond differently to therapies and more than one trial may be necessary
- Treatment is intended to stimulate the nasopharyngeal reflexes and cranial nerves involved in the hiccough reflex arc. They may need to be tried several times to be successful.
- Non-pharmacologic treatments exist and should be tried first
  - Holding breath
  - Breathe out against your closed mouth/nose
  - Breathing into a bag
  - Peppermint
  - Stimulate the back of the throat by swallowing 1 teaspoon of sugar, gargling water
  - Attempt to increase vagal tone through: Valsalva maneuver, digital orbital pressure, digital rectal massage
  - Sour taste is hypothesized to irritate the soft palate which can treat hiccoughs. A sip of vinegar, angoustura bitters, or sucking the juice of lemon have been successful in single case studies.
  - Intranasal administration of 0.1ml of vinegar with a plastic oral syringe has been reported to be effective in several case reports of palliative care patients

- » Consider acupuncture if intolerable medication side effects prohibit continued drug use

- Pharmacological Therapy:
  - » 1st Step: Treat underlying cause
    - ° GERD: H2RA (ex: ranitidine, famotidine) or PPI (ex: omeprazole, pantoprazole)
    - ° Infection: appropriate antibiotic
    - ° Correct electrolyte abnormalities
  - » 2nd Step: Reduce gastric distension
    - ° Simethicone, metoclopramide
  - » 3rd Step: Suppression of Reflex Arc and reduce diaphragm irritation
    - ° Use medications such as baclofen, chlorpromazine, haloperidol, metoclopramide, midazolam, nifedipine, valproic acid
    - ° Single case studies have shown potential benefit with medications such as chlordiazepoxide, lorazepam, olanzapine, quinidine, lidocaine, amantadine, or ketamine.
  - » Intractable Hiccoughs
    - ° Chlorpromazine IV
    - ° Nerve block, crush, or stimulation
    - ° Palliative sedation is last line therapy

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DOPAMINE ANTAGONIST				
Chlorpromazine (Thorazine)	Initial: 25-50mg TID-QID MDD: 200mg/day	Solution for injection: 25mg/ml Tablet: 10mg, 25mg, 50mg, 100mg, 200mg	• Acute relief: 1 time dose of 10-25mg PO • While this is the only medication with FDA approved hiccups indication, there is limited evidence of efficacy • More sedating than haloperidol • Avoid in Parkinson or dementia with Lewy body disease • If symptoms persist, then consider 25-50mg via slow IV infusion • Side effects: orthostasis, urinary retention, sedation • Expensive	Y
Haloperidol (Haldol)	Initial: 2-5mg (PO/SQ) for loading dose, then 1-4mg TID MDD: not established for this indication	Oral solution: 2mg/ml Solution for injection (lactate): 5mg/ml Tablet: 0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg	• Mechanism of action: treating irregular spasmodic movement of muscle • Case reports show successful management with varied response times (30 minutes to 24 hours) • Good alternative to chlorpromazine, better tolerated (especially if sedation occurred) • Avoid in Parkinson or dementia with Lewy body disease • PO:INJ (lactate) is 2:1 • Injection is expensive	Y
PROKINETIC				
Metoclopramide (Reglan)	Initial: 5-10mg IV q 8hrs OR 10mg orally q6-8 hrs MDD: 30mg/day	Oral disintegrating tablet (ODT): 5mg Oral solution: 5mg/5ml, 10mg/ml Solution for injection: 5mg/ml Tablet: 5mg, 10mg	• Acute relief: 1 time dose of 10mg PO • Effective for hiccups secondary to gastric distention or GERD • Promotes gastric emptying • Chronic use has been associated with tardive dyskinesia. Monitor for extrapyramidal symptoms	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTI-FLATULENT				
Simethicone (Gas-X)	Initial: 40-125mg QID (AC & HS) MDD: 500mg/day	Capsule: 125mg, 180mg, 250mg Chewable tablet: 80mg, 125mg Oral disintegrating strip: 40mg, 62.5mg Oral suspension: 20mg/0.3ml, 40mg/0.6ml	• Effective for hiccups secondary to gastric distension	Y
SKELETAL MUSCLE RELAXANT				
Baclofen (Lioresal)	Initial: 5-20mg up to QID MDD: 80mg/day	Tablet: 10mg, 20mg	• Acute Relief: 1 time dose of 5mg PO • Inhibits synaptic reflexes at spinal level • Effective for hiccups secondary to intercostal muscle contraction • Caution with renal dysfunction	Y
Cyclobenzaprine (Flexiril)	Initial: 5mg TID MDD: 30mg/day	Capsule (ER):* 15mg, 30mg Oral suspension: 1mg/ml Tablet: 5mg, 7.5mg, 10mg	• Can cause drowsiness and xerostomia (anticholinergic)	Y/N*
BENZODIAZEPINES				
Diazepam (Valium)	Initial: 2mg IV/PO/IM/PR QID MDD: 40mg/day	Oral solution: 5mg/ml Solution for injection: 5mg/ml Tablet: 2mg, 5mg, 10mg	• May cause hiccoughs, monitor for paradoxical worsening • Can be given IV; PO:INJ is 1:1 • Long acting, active metabolites may accumulate and contribute to sedation, especially in elderly patients • Oral solution is more expensive than tablets	Y
Midazolam (Versed)	Initial: 10-15mg IV (Loading Dose) 40-120mg/24 hr SQ infusion (maintenance) MDD: 120mg/day	Oral solution: 2mg/ml Solution for injection: 2mg/2ml, 5mg/5ml, 5mg/ml, 10mg/10ml, 10mg/2ml, 25mg/5ml, 50mg/10ml	• Last line of therapy due to sedation • Other benzodiazepines can be used (lorazepam) • May cause hiccoughs, monitor for paradoxical worsening	N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICONVULSANTS				
Carbamazepine (Tegretol)	Initial: 200mg QD-TID MDD: Not established for this indication	Capsule (ER)*: 100mg, 200mg, 300mg Chewable tablet: 100mg Oral suspension: 100mg/5ml Tablet: 200mg Tablet (ER)*: 100mg, 200mg, 400mg	• Consider use if brain tumor is suspected cause of hiccoughs • GI side-effects may be minimized by taking with food or reducing the dose • Many drug interactions (enzyme inducer) • ER caps can be opened, but contents should not be crushed	Y/N*
Divalproex (Depakote)	Initial: 15mg/kg/ day; May increase dose by 250mg every 2 weeks until hiccups subside or medication is no longer tolerated (maintenance) MDD: Patient specific	Sprinkle capsule (DR): 125mg Tablet (DR)*: 125mg, 250mg, 500mg Tablet (ER)*: 250mg, 500mg	• Acute Relief: 1 time dose of 250-500mg PO • Consider use if brain tumor is suspected cause of hiccoughs • Tolerance to GI side effects develops within 1-2 weeks • Postural tremor is a common adverse effect • Contraindicated if significant liver disease • Approximately 1:1 conversion between valproic acid and divalproex DR • Sprinkle capsules may be opened, but contents should be swallowed whole	Y/N*
Valproic Acid (Depakene)	Initial: 15mg/kg/ day; May increase dose by 250mg every 2 weeks until hiccups subside or medication is no longer tolerated (maintenance) MDD: Patient specific	Capsule: 250mg Oral Syrup: 250mg/5ml Solution for injection: 100mg/ml	• Acute Relief: 1 time dose of 250-500mg PO • Consider use if brain tumor is suspected cause of hiccoughs • Tolerance to GI side effects develops within 1-2 weeks • Postural tremor is a common adverse effect • Contraindicated if significant liver disease • Approximately 1:1 conversion between valproic acid and divalproex DR *(Continued on next page)*	N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICONVULSANTS (CONTINUED)				
Gabapentin (Neurontin)	Initial: 300-600 TID; Titrate to response. MDD: Not established for this use	Capsule: 100mg, 300mg, 400mg Oral solution: 250mg/5ml Tablet: 600mg, 800mg	• Acute/burst Relief: 400mg TID x 3 days, then 400mg QD x 3 days, then stop • Dose at 900-1200mg/day were shown to be effective • May be beneficial when there is brain stem ischemia or inflammation • Side Effects: drowsiness	Y
Phenytoin (Dilantin)	Initial: 200mg slow IV push, then 300-400mg QD in divided doses MDD: Not established for this indication	Capsule (ER): 100mg, 200mg, 300mg Chewable tablet: 50mg Oral suspension: 100mg/4ml, 125mg/5ml Solution for injection: 50mg/ml	• Useful for patients with a hiccoughs etiology related to CNS (inhibits motor activity) • Consider use if brain tumor is suspected cause of hiccoughs • Highly protein-bound and increased effect expected with renal failure, hyperbilirubinemia, and hypoalbuminemia • Many drug interactions (enzyme inducer) • Oral suspension binds to tubes • IM PR route not recommended due to poor/ erratic absorption and adverse effects • Adverse effects are concentration dependent	Y/N*
CARDIAC MEDICATIONS				
Carvedilol (Coreg)	Initial: 6.25mg QID MDD: Not established for this indication	Capsule (CR): 10mg, 20mg, 40mg, 80mg Tablet: 3.125mg, 6.25mg, 12.5mg, 25mg	• Not appropriate for patients with hypotension and bradycardia • Used for treatment of tardive dyskinesia and shown to be helpful for hiccough	Y
Nifedipine (Adalat, Procardia)	Initial: 10-20mg q 8H MDD: 80mg/day	Capsule: 10mg, 20mg Tablet (ER)*: 30mg, 60mg, 90mg	• Acute Relief: 1 time dose 10mg PO • Not appropriate for patients with hypotension • Monitor blood pressure	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CORTICOSTEROIDS				
Dexamethasone (Decadron)	Initial: Not established MDD: Not established for this indication	Oral solution: 0.5mg/5ml, 1mg/ml Solution for injection: 4mg/ml, 10mg/ml Tablet: 0.25mg, 0.5mg, 0.75mg, 1mg, 1.5mg, 2mg, 4mg, 6mg	• Single reference suggested 40mg QD • Has shown to cause persistent hiccoughs, use with caution • Give last dose by 2pm to avoid steroid induced insomnia • Use with caution in diabetics due to resultant hyperglycemia • May cause GI upset; take with food or milk	Y
Prednisone (Orasone)	Initial: 10-40mg MDD: 60mg/day	Oral solution: 1mg/ml, 5mg/ml Tablet: 1mg, 2.5mg, 5mg, 10mg, 20mg, 50mg	• Use if tumor involvement or hepatomegaly • Use with caution in diabetics due to resultant hyperglycemia • May cause GI upset; take with food or milk	Y
ANTIDEPRESSANTS				
Amitriptyline (Elavil)	Initial: 25-90mg QD MDD: Not established for this indication	Tablet: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	• Tricyclic antidepressant • Increase risk of falls • Anticholinergic side effects	Y
Sertraline (Zoloft)	Initial: 50mg QD MDD: 200mg/day	Oral solution: 20mg/ml Tablet: 25mg, 50mg, 100mg	• SSRI • Use lower doses in hepatic impairment	Y
STIMULANTS				
Methylphenidate (Ritalin)	Initial: 5-20mg QD MDD: Not established for this indication	Tablet: 5mg, 10mg, 20mg	• Acute Relief: 1 time dose of 5mg PO • Use with caution in patients with cardiac disease or uncontrolled hypertension	Y

References

- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 667-9.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 267-270.
- Chang FY, Lu CL. Hiccup: Mystery, Nature, and Treatment. J Neurogastroenterol Motil 2012;18:123-130
- Farmer, C. Management of Hiccups, Fast Fact #81 CAPC, accessed online at: https://www.capc.org/fast-facts/81-management-hiccups/
- Ferdinand P, Oke A. Intractable Hiccups Post Stroke: Case Report and Review of the Literature. J Neurol Neurophysiol 2012, 3(5)
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 101.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 825-8.
- Kako, J. et al. Intranasal vinegar as an effective treatment for persistent hiccups in a patient with advanced cancer undergoing palliative care, JPSM, 2017; article in press:e1-2.
- Launois S, Bizec JL, Whitelaw WA, et al. Hiccup in adults: an overview. Eur Resplr J, 1993, 8, 583-575
- Lembo, A. et al. Overview of hiccups, UpToDate, literature review current through Nov. 2015.
- Lexi-comp 5-min. consults: Hiccoughs. Accessed August 26, 2015.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 195-196.
- Smith HS, Busracamwongs A. Management of hiccups in the palliative care population. Am J Hosp Palliat Care. 2003 Mar-Apr;20(2):149-54.
- Stueber D, Swartz CM. Carvedilol Suppresses Intractable Hiccups, J Am Board Fam Med 2006;19:418 –21.
- Watson M, Lucas C, Hoy A, Back I, Armstrong P. Hiccups Palliative Adult Network Guidelines. 3rd Ed. 2011. Pg 99, accessed online Nov. 2015 at: http://book.pallcare.info/
- Woelk, CJ. Managing hiccups. Palliative Care Files. Canadian Family Physician. June 2001; 57: 672-675

Insomnia

DEFINITION

Insomnia is a persistent, subjective complaint related to sleep initiation, duration consolidation, or quality that occurs despite an adequate opportunity for sleep, and results in some form of daytime impairment. This includes complaints of difficulty falling asleep, frequent nighttime awakenings, difficulty returning to sleep once awake, awakening too early, or sleep that is not restful or restorative.

CAUSES

- Poorly controlled symptoms or medical conditions (Ex: pain, depression, anxiety, stress/worry, delirium, urinary frequency, fever, dyspnea/sleep apnea, nausea/vomiting, restless legs syndrome, GERD, thyroid dysfunction, dementia)
- Environmental factors (unfamiliar environment, uncomfortable temperature, noise, light, distractions from other patients, interruptions for lab/vitals monitoring)
- Medication use (psychostimulants, bronchodilators, corticosteroids, select antihypertensives, SSRIs (particularly fluoxetine if taken late in the day), SNRIs, dopamine agonists, anticonvulsants, diuretics, thyroid hormones, decongestants, nicotine replacement therapy)
- Medication or other substance withdrawal (alcohol, hypnotics, analgesics, illicit drugs)
- Poor sleep hygiene (Ex: going to bed without intending to go to sleep immediately, taking daytime naps)
- Dietary (caffeine and/or alcohol use, large meals and/or excessive fluids prior to bedtime)
- Smoking or other nicotine use (particularly in the evening)
- Not enough daytime exercise/ exercise too late in the day

HOW TO RECOGNIZE SYMPTOM

- Frequently ask the patient if they are experiencing sleep disturbances
- Complaints of poor sleep quality or quantity despite adequate time for sleep
- Daytime fatigue
- Irritability
- Decreased concentration

CLINICAL INSIGHTS

- Normal sleep patterns include initiating sleep when desired, maintaining sleep and waking when desired
- While non-pharmacologic interventions (such as maintaining a regular sleep schedule, adjusting the bedroom environment and avoiding daytime naps) by themselves have not been found to be effective, it is recommended that they be used as part of a broad treatment plan
- The 1st step in treating insomnia is to attempt to identify and treat any potentially precipitating causes, keeping in mind there may be more than one.
- Insomnia is associated with an increased risk of anxiety, depression and complaints of pain
  - » Symptoms may relate to each other in cyclical fashion. For example, pain can result in insomnia; insomnia can result in decreased pain threshold.
- The timing, characteristics of symptoms, and comorbidities should guide choice in sedative, for example:
  - » Anxiety commonly prevents falling asleep and may respond to benzodiazepines
  - » Early awakening is a sign of depression and this type of insomnia may respond better to a sedating antidepressant.
- When possible, choose a sedative that treats more than one symptom that a patient is experiencing to reduce pill burden, adverse effects, drug interactions and spend. Examples of multi-use medication opportunities when treating insomnia include:
  - » Benzodiazepines – anxiety, spasticity (diazepam), seizure (diazepam, lorazepam)
  - » Tricyclic antidepressants – depression, neuropathic pain, sialorrhea, itching (doxepin)

  - » Mirtazapine – depression, itching, anorexia, anxiety, pain
  - » Antihistamines – itching
  - » Antipsychotics – psychosis (hallucination/delirium), sundowning, agitation

- Current guidelines advise against the chronic use of OTC products because of their inconsistent efficacy and adverse effect profile
- The use of herbal substances, such as Valerian, is not recommended for insomnia
- Most medications that could potentially be used for the treatment of insomnia carry significant risks of adverse effects, particularly in elderly patients; careful analysis of risk: benefit should be performed prior to use.
- Benzodiazepines commonly worsen dementia related symptoms and behaviors and are associated with confusion, falls, fractures, delirium in elderly patients.
- Halcion (Triazolam) will not help patients stay asleep and is associated with rebound insomnia due to its short half-life
- Flurazepam and quazepam should be avoided due to active metabolites, leading to long durations of action and increased adverse effects, including excessive a.m. sedation.
- Zolpidem, eszopiclone, and zaleplon are not more effective than benzodiazepine sedative hypnotics, but are more expensive and lack anxiolytic effects.
- Secondary side chain tricyclic antidepressants (nortriptyline, desipramine) have fewer anticholinergic adverse effects than those with tertiary side chains (doxepin, amitriptyline) and should be used unless anticholinergic properties used to therapeutic advantage.
- If anxiety is identified as a precipitating cause of insomnia, any benzodiazepine may be potentially effective promoting sleep.
- In the absence of delirium or psychosis, antipsychotics have not been shown to be effective and should be avoided for treatment of insomnia.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BENZODIAZEPINES				
Estazolam (Prosom)	Initial: 1mg PO at bedtime MDD: 2mg/day	Tablet: 1mg, 2mg	• In small or debilitated older patients, a starting dose of 0.5mg should be considered	Y
Temazepam (Restoril)	Initial: 7.5mg PO at bedtime MDD: 30mg/day	Capsule: 7.5mg, 15mg, 22.5mg, 30mg	• Can be given scheduled or PRN • Good to maintain sleep cycle • Tolerance less likely to develop than with other benzodiazepines; reportedly maintains hypnotic effect for at least 1 month of continued use • 7.5mg, 22.5mg capsule significantly more expensive	Y
Triazolam (Halcion)	Initial: 0.125mg PO at bedtime MDD: 0.5mg/day (0.25mg/day if elderly)	Tablet: 0.125mg, 0.25mg	• Very short duration of effect; useful for promoting, but not maintaining sleep • Tolerance develops after 2 weeks of continuous use	Y
NON-BENZODIAZEPINE SEDATIVE HYPNOTICS				
Eszopiclone (Lunesta)	Initial: 1mg PO at bedtime MDD: 3mg/day	Tablet: 1mg, 2mg, 3mg	• Associated with unintentional sleep-related activities (sleepwalking, etc.) • Avoid co-administration with high fat meals (delayed absorption, onset) • Commonly causes bitter taste (30%) • More expensive than other agents	Y
Zaleplon (Sonata)	Initial: 5mg PO at bedtime MDD: 20mg/day (10mg/day if elderly)	Tablet: 5mg, 10mg	• Associated with unintentional sleep-related activities (sleepwalking, etc.) • Very short half-life; effective for promoting, but not maintaining sleep • Due to short half-life, may take at any point when insomnia occurs, not just at bedtime • More expensive than other agents	Y
Zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist)	Initial (IR): 5mg PO at bedtime Initial (CR): 6.25mg MDD (IR): 10mg/day MDD (CR): 12.5mg/day	Oral spray (Zolpimist Brand): 5mg per spray Tablet: 5mg, 10mg Tablet (CR)*: 6.25mg, 12.5mg Tablet (SL) (Edluar Brand): 5mg, 10mg Tablet (SL) (Intermezzo Brand): 1.75mg, 3.5mg	• Women and elderly patients should not exceed 5mg daily • Associated with unintentional sleep-related activities (sleepwalking, etc.) • Intermezzo only form of zolpidem approved for middle of night awakening; can be used if planned 4 hours of sleep remaining • More expensive than other agents	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MELATONIN RECEPTOR AGONISTS				
Melatonin	Initial: 0.5-5mg MDD: not established for this indication	Tablet: 1mg, 3mg, 5mg	• Safer, but less effective than other agents • Limited data to support use or effectiveness • Not FDA approved for treatment of insomnia • Therapeutic effect thought to be due to suppression of arousal-promoting impulses from the hypothalamus	Y
Ramelteon (Rozerem)	Initial: 8mg PO at bedtime MDD: 8mg/day	Tablet: 8mg	• Use with caution in elderly • Modest improvement in sleep onset, but ineffective for sleep maintenance • Not a controlled substance • More expensive than other agents	N
Tasimelteon (Hetlioz)	Initial: 20mg PO QHS MDD: 20mg/day	Capsule: 20mg	• Restricted distribution in U.S. • Indicated only for non-24-hour sleep-wake disorder • Take on an empty stomach	N
ANTIDEPRESSANTS				
Amitriptyline (Elavil)	Initial: 25-75mg PO at bedtime (10-25mg if elderly) MDD: 300mg/day	Tablet: 10mg, 25mg, 50mg, 75mg,100mg, 150mg	• May increase dose by 25mg q1-2 weeks if needed • Consider if comorbid depression • Increase risk of falls • Most anticholinergic of all TCAs	Y
Desipramine (Norpramin)	Initial: 25-75mg PO at bedtime (10-25mg if elderly) MDD: 300mg/day	Tablet: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	• May increase dose by 25mg q1-2 weeks if needed • Consider if comorbid depression • Increase risk of falls • Least anticholinergic of all TCAs; better tolerated in elderly patients than other TCAs	Y
Doxepin (Sinequan, Silenor)	Initial: 3-25mg PO QHS MDD: 300mg/day	Capsule: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg Oral solution: 10mg/ml Tablet (brand only): 3mg, 6mg	• Use with caution in elderly • Consider if comorbid depression • Only antidepressant approved for treatment of insomnia • Consider the 10mg generic capsule or oral solution if lower doses targeted to avoid high cost w/ brand tablet • Doses ≤ 6mg safer in elderly patients (AGS Beers criteria) *(Continued on next page)*	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIDEPRESSANTS (CONTINUED)				
Mirtazapine (Remeron)	Initial dose: 7.5mg MDD: higher doses become less sedating	Solutab: 15mg, 30mg, 45mg Tablet: 7.5mg, 15mg, 30mg, 45mg	• Consider in patients with other symptoms that may benefit from use, including: depression, anorexia, itching, anxiety, pain • More sedating at lower doses (7.5-15mg)	Y
Nortriptyline (Pamelor)	Initial: 25-50mg PO at bedtime (10-25mg if elderly) MDD: 150mg/day	Oral solution: 10mg/5ml Tablet: 10mg, 25mg, 50mg, 75mg	• May increase dose by 25mg q1-2 weeks • Consider if comorbid depression • Increase risk of falls • Least anticholinergic of all TCAs; better tolerated in elderly patients than other TCAs	Y
Trazodone (Desyrel)	Initial: 25-50mg PO at bedtime Range: 50-100mg MDD: 600mg/day	Tablet: 50mg, 100mg, 150mg, 300mg	• Drug of choice for patients taking benzodiazepines • Often added for antidepressant-induced insomnia • Priapism is a rare, but serious ADE • Consider if comorbid depression	Y
ANTIHISTAMINES				
Diphenhydramine (Benadryl)	Initial: 25-50mg PO at bedtime MDD: 400mg/day	Capsule: 25mg, 50mg Elixir: 12.5mg/5ml Solution for injection: 50mg/ml Tablet: 25mg, 50mg	• Avoid in elderly patients due to potential for anticholinergic adverse effects such as delirium • Useful if itching contributing to insomnia • Tolerance can develop rapidly with routine use; efficacy similar to placebo after 4 days of continuous use. This may be avoided with limited, occasional PRN use.	Y
Hydroxyzine (Atarax, Vistaril)	Initial: 10-100mg PO at bedtime MDD: 100mg/day	Capsule: 25mg, 50mg, 100mg Oral suspension: 25mg/5ml Solution for injection: 25mg/ml, 50mg/ml Tablet: 10mg, 25mg, 50mg	• Avoid in elderly patients due to potential for anticholinergic adverse effects such as delirium • Useful if itching or anxiety contributing to insomnia	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OREXIN RECEPTOR ANTAGONIST				
Suvorexant (Belsomra)	Initial: 10mg PO QHS MDD: 20mg/day	Tablet: 5mg, 10mg, 20mg	• For sleep onset or maintenance • Use lowest effective dose • Requires dose adjustment if concomitant moderate CYP3A4 inhibitors • Contraindicated if concomitant strong CYP3A4 inhibitor use • Take on an empty stomach • Can cause behavioral changes	Y
OTHER				
Chloral Hydrate (Somnote)	Initial: 500-1,000mg PO at bedtime (250mg if elderly) MDD: 2,000mg/day	Capsule: 500mg Suppository: 325mg, 650mg Syrup: 500mg/5ml	• Should be reserved for when all other agents have failed • Most effective dose 1,000mg	Y

References

- Bain, K., et al, Toward evidence-based prescribing at end of life: A comparative review of temazepam and zolpidem for the treatment of insomnia, J. of Hospice and Palliative Care, Vol. 20(5) September/October 2003.
- Bonnet, M. et al. Clinical features and diagnosis of insomnia, UpToDate, literature review current through Nov. 2015.
- Bonnet, M. et al. Overview of insomnia, UpToDate, literature review current through Nov. 2015.
- Bonnet, M. et al. Treatment of insomnia, UpToDate, literature review current through Nov. 2015.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 664,701-2.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 200-201.
- Emanuel, LL, et al, Self-study Module 3l – Insomnia. EPEC-O Education in Palliative and End-of-Life Care – Oncology, 2005. Accessed online 2/26/14 at: [http://www.cancer.gov/cancertopics/cancerlibrary/epeco/selfstudy/module-3/module-3l-pdf]
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3l: Insomnia, accessed online Nov. 2015 at: http://www.cancer.gov/resources-for/hp/education/epeco/self-study/module-3/module-3l.pdf
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 108.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 1064-6, 1070-7, 1477.
- Hirst, J. et al. Overview of insomnia in palliative care, UpToDate, literature review current through Nov. 2015.
- Hugel, H., et al, The Prevalence, Key Causes and Management of Insomnia in Palliative Care Patients, J. of Pain and Symptom Management, Vol. 27(4) April 2004.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Sateia, Michael J., et al, Sleep in Palliative Care, Oxford Textbook of Palliative Medicine, 4th ed., 2010, pages 1059-1077.
- Wells, Barbara G. et al, Pharmacotherapy Handbook, 8th ed. 2012, pages 911-920.

Itching / Pruritus

DEFINITION

Itching is the uncomfortable physiological and pathological sensation arising from irritated skin or mucous membranes causing an urge to scratch or rub affected areas.

CAUSES

- Environmental
  - » Dry Skin/eczema
  - » Exposure to heat/moisture
- Infection
  - » Fungal/bacterial skin Infection
- Allergic reaction / hives
- Organ failure
  - » Liver disease (eg, hepatitis, cholestasis, primary biliary cirrhosis)
  - » Kidney disease/uremia – most common with stages 4 and 5 (ESRD)
- Malignant
  - » Paraneoplastic syndromes
  - » Hematologic malignancy
  - » Solid tumors
  - » Skin malignancy
  - » Lymphoma
  - » Multiple myeloma
- HIV/AIDS
- Neurological
  - » Central lesions / Multiple Sclerosis
  - » Peripheral neuropathy
- Endocrine diseases
  - » Diabetes
  - » Thyroid dysfunction
- Iron deficiency anemia
- Medications: opioids, antifungals, alprazolam, amlodipine, bicalutamide, bupropion, donepezil, megestrol, tramadol, anti-infectives

HOW TO RECOGNIZE SYMPTOM

- Patients may be seen itching, rubbing, or tapping skin
- May describe sensations of burning, tingling, numbness, or objects crawling on the skin
- Skin may be dry, flaky, swollen, red, inflamed or hives may be present

CLINICAL INSIGHTS

- Non-pharmacological measures should be considered, regardless of the suspected cause of itching
  - » Dry skin should be treated regularly with moisturizing lotion 2-3 times per day
  - » Avoid soaps that may dry the skin
  - » Consider a humidifier to moisten the air
  - » Cool compresses and oatmeal baths may provide temporary relief
  - » Keep nails trimmed / consider wearing cotton gloves at night to minimize injury from scratching
  - » Consider UVB therapy for uremic pruritus
- Treat / remove underlying causes if possible / identifiable
  - » Opioid induced pruritus is more likely to occur with morphine, codeine, and oxycodone. If one opioid is suspected, rotation to a different opioid is appropriate.
  - » Review medication profile for recently added drugs
- Choice of pharmacological agent should be based on suspected underlying cause of itch
- Consider initial management of localized itch with topical agents. Generalized itching will likely require therapy with systemic agents.
- Antihistamines are most effective for itching due to allergy, but are not typically effective for itching due to liver or kidney disease other than by providing a sedative effect
- Pruritus associated with liver cirrhosis typically begins on the palms of hands and soles of feet and often peaks between noon and 4:00PM
- For patients with ESRD, continued use of phosphate binders may be reasonable to provide relief of itch
- Some agents have evidence to support efficacy, but are cost-prohibitively expensive in the hospice setting

- Oral 17α-alkyl androgens such as methyltestosterone and danazol have been used for itch due to cholestasis, but their availability is limited
- Oral thalidomide has been used for itch due to uremic pruritus

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DUE TO ALLERGIC REACTION/ HIVES				
Diphenhydramine (Benadryl)	Initial: 25-50mg BID-QID MDD: 400mg/day	Capsule: 25mg, 50mg Oral solution: 12.5mg/5ml Solution for injection: 50mg/ml Tablet: 25mg, 50mg	• Sedating antihistamine • Anticholinergic properties: confusion, constipation, dizziness, dry mouth, urinary retention	Y
Hydroxyzine HCl or Pamoate (Atarax, Vistaril)	Initial: 25mg TID-QID PRN MDD: 400mg/day	Capsule (pamoate): 25mg, 50mg, 100mg Oral solution: 25mg/ml, 50mg/ml Tablet (HCl): 10mg, 25mg, 50mg	• Sedating • Antihistamine with anxiolytic properties • Vistaril is less expensive than Atarax	Y
Methylprednisolone (Medrol)	Initial: 4-48mg per day divided QD-QID or 24mg as day one of dosepak MDD: 48mg/day	Tablet: 2mg, 4mg, 6mg, 8mg, 16mg, 32mg	• Avoid administering in evening, may cause insomnia • May cause G.I. upset; take with food or milk	Y
Prednisone (Deltasone)	Initial: 10-60mg daily in divided doses MDD: 60mg/day	Oral solution: 1mg/ml, 5mg/ml Tablet: 1mg, 2.5mg, 5mg, 10mg, 20mg, 50mg	• Avoid administering in evening, may cause insomnia • Avoid abrupt withdrawal • May cause G.I. upset; take with food or milk	Y
DUE TO CORTICOSTEROID RESPONSIVE DERMATOSES				
Hydrocortisone Topical (Westcort, others)	Initial: Apply sparingly to affected area BID-QID MDD: not established	Cream: 0.5%, 1% Gel: 1% Lotion: 1% Ointment: 0.5%, 1%, 2.5%	• Use smallest amount necessary to cover affected area • Avoid applying to irritated or broken skin • Prolonged use may cause thinning of skin	-
Triamcinolone Acetonide Topical (Kenalog, others)	Initial: Apply sparingly to itchy area BID-QID MDD: not established	Cream: 0.025%, 0.1%, 0.5% Lotion: 0.025%, 0.1% Ointment: 0.025%, 0.1%, 0.5%	• Use smallest amount necessary to cover affected area • Avoid applying to irritated or broken skin • Prolonged use may cause thinning of skin	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DUE TO LIVER DISEASE/ CHOLESTASIS				
Betamethasone Diproprionate (Diprolene, others)	Initially: Apply sparingly to itchy area QD-BID MDD: not established	Cream: 0.05% Gel: 0.05% Lotion: 0.05% Ointment: 0.05%	• Use smallest amount necessary to cover affected area • Avoid applying to irritated or broken skin • Prolonged use may cause thinning of skin	-
Betamethasone Valerate Topical (Luxiq, others)	Initially: Apply sparingly to itchy area QD-BID MDD: not established	Cream: 0.1% Lotion: 0.1% Ointment: 0.1%	• Use smallest amount necessary to cover affected area • Avoid applying to irritated or broken skin • Prolonged use may cause thinning of skin	-
Paroxetine (Paxil)	Initial (IR): 10-20mg QAM Initial (ER): 12.5-25mg PO QAM MDD (IR): 50mg/day (40mg if elderly or hepatic impairment) MDD (ER): 62.5mg/day (50mg if elderly or hepatic impairment)	Oral suspension: 10mg/5ml Tablet: 10mg, 20mg, 30mg, 40mg Tablet (CR)*: 12.5mg, 25mg, 37.5mg	• Onset typically observed after 2-3 days • Antipruritic effect may wear off in a few weeks	Y/N*
Sertraline (Zoloft)	Initial: 50mg PO QD MDD: 100mg/day (dose adjusted for liver disease)	Oral solution: 20mg/ml Tablet: 25mg, 50mg, 100mg	• Limited evidence based on retrospective analysis • Typical effective dose was 50-100mg/day	Y
Cholestyramine (Questran)	Initial: Mix and drink 4 grams in 60-180ml of non-carbonated liquid QD-BID MDD: 16g/day	Powder: 4g/packet or scoop	• First line therapy • Administer other medications 1 hour before or 4-6 hours after cholestyramine • Palatability may be improved if liquid is refrigerated • May cause constipation; consider administration with a laxative • Ineffective if complete bile duct obstruction (grey colored stools are indicative) *(Continued on next page)*	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DUE TO LIVER DISEASE/ CHOLESTASIS (CONTINUED)				
Lidocaine Inj. (Xylocaine)	Initial: 100mg in 5ml saline IV infusion over 5 minutes MDD: not established	Solution for injection: 0.5%, 1%, 1.5%, 2%, 4%	• May offer prolonged relief of itching • Transient tinnitus or paresthesias may occur during infusion • May cause initial worsening of pruritus prior to clinical improvement	-
Mirtazapine (Remeron)	Initial: 15mg PO QHS MDD: 45mg/day	Oral disintegrating tablet (ODT): 15mg, 30mg, 45mg Tablet: 15mg, 30mg, 45mg	• Limited evidence based on case report(s) • Itching may improve in as little as 24 hours • Titrate after 1 week if partial response observed	Y
Naloxone (Narcan)	Initial: IV bolus of 0.4mg in 1ml saline followed by IV infusion of 0.2mcg/kg/min in 5% dextrose/0.45%NaCl infused over 24 hours (total volume infused 500ml/24 hours) MDD: Not established for this indication	Solution for injection: 0.4mg/ml, 1mg/ml	• Contraindicated if receiving opioids • Dose for itching higher than dose needed to reverse opioid overdose • May cause opioid withdrawal symptoms (even if not receiving opioids)	-
Naltrexone (Revia, Vivitrol)	Initial: 50mg PO QD MDD: Not established for this indication	Suspension for injection: 380mg Tablet: 50mg	• Contraindicated if receiving opioids • May cause opioid withdrawal symptoms (even if not receiving opioids)	Y
Ondansetron (Zofran)	Initial: 8mg PO TID MDD: 24mg/day	Oral Disintegrating Tablet (ODT): 4mg, 8mg Oral film: 4mg, 8mg Oral solution: 4mg/5ml Solution for injection: 4mg/2ml Tablet: 4mg, 8mg	• May offer significant, but moderate symptom improvement • Conflicting evidence to support use • Expensive	Y
Propofol (Diprivan)	Initial: 15mg IV QD MDD: not established for this indication	Emulsion for injection: 10mg/ml	• Requires specialized training / equipment • Doses used for itching much less than for anesthesia *(Continued on next page)*	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DUE TO LIVER DISEASE/ CHOLESTASIS (CONTINUED)				
Dronabinol (Marinol)	Initial: 5mg PO QHS MDD: 20mg/day	Capsule: 2.5mg, 5mg, 10mg	• Based on small case series • Duration of effect observed as 4-6 hours, so more frequent dosing should be considered if response to initial dosing • Expensive	N
Midazolam (Versed)	Initial: 2mg IV/SQ bolus, then 1mg/hr infusion MDD: not established for this indication	Solution for injection: 1mg/ml, 5mg/ml Syrup: 2mg/ml	• Consider if alternate therapies have failed and sedation is desired • Can potentially be titrated to improve itching without over sedating	-
Phenobarbital (Luminal)	Initial: 60mg PO BID MDD: titrate to serum level greater than 10mcg/ml	Elixir: 20mg/5ml Solution for injection: 65mg/ml, 130mg/ml Tablet: 15mg, 16.2mg, 30mg, 32.4mg, 60mg, 64.8mg, 97.2mg, 100mg	• May enhance excretion of substances that cause itching by hepatic enzyme induction • Typical doses studied ranged from 120-250mg per day • Sedation is common • Interacts with a number of medications (enzyme inducer) • Avoid if hepatic encephalopathy • Solution for injection is expensive	Y
Rifampin (Rifadin)	Initial: 300-600mg/day divided BID-TID MDD: 600mg/day	Capsule: 150mg, 300mg Solution for injection: 600mg reconstituted	• Superior to phenobarbital in comparative trial • May enhance excretion of substances that cause itching by hepatic enzyme induction • Interacts with a number of medications (enzyme inducer)	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DUE TO UREMIC PRURITUS				
Activated charcoal (Actidose, Kerr Insta-char)	Initial: 5-6 grams QD MDD: not established for this indication	Capsule: 260mg Oral suspension: 25g/120ml	• Often combined with sorbitol	-
Capsaicin (Zostrix, others)	Initial: 0.025% cream topically to affected area QID MDD: not established for this indication	Cream: 0.025%, 0.075%, 0.25% Gel: 0.025%, 0.05%, 0.075% Lotion: 0.035% Patch: 8% Stick: 0.075%	• Reserve use for localized pruritus • Poorly tolerated; causes local burning sensation during first few days of treatment • Delayed onset of several weeks; avoid initiating therapy in patients ceasing dialysis	-
Cholestyramine (Questran)	Initial: Mix and drink 4 grams in 60-180 ml of non-carbonated liquid QD-BID MDD: 16g/day	Powder: 4g/packet or scoop	• Administer other medications 1 hour before or 4-6 hours after cholestyramine • Palatability may be improved if liquid is refrigerated • May cause constipation; consider administration with a laxative	-
Mirtazapine (Remeron)	Initial: 15mg PO QHS MDD: 45mg/day	Oral disintegrating tablet (ODT): 15mg, 30mg, 45mg Tablet: 15mg, 30mg, 45mg	• Limited evidence based on case report(s) • Itching may improve in as little as 24 hours • Titrate after 1 week if partial response observed	Y
Naloxone (Narcan)	Initial: 0.25mcg/kg/hour IV MDD: not established for this indication	Solution for injection: 0.4mg/ml, 1mg/ml	• Conflicting evidence to support use • Contraindicated if receiving opioids • Dose for itching higher than dose needed to reverse opioid overdose • May cause opioid withdrawal symptoms (even if not receiving opioids)	-
Ondansetron (Zofran)	Initial: 4mg PO BID MDD: 24mg/day	Oral disintegrating tablet (ODT): 4mg, 8mg Oral film: 4mg, 8mg Oral solution: 4mg/5ml Solution for injection: 4mg/2ml Tablet: 4mg, 8mg	• Conflicting evidence to support use • May consider once daily rectal administration of 16mg dose • Expensive *(Continued on next page)*	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DUE TO UREMIC PRURITUS (CONTINUED)				
Polidocanol Containing Agents (Balneum medicinal bath oil)	Initial: 30-45ml for full bath MDD: : not established for this indication	Bath oil	• Conflicting evidence to support use	-
Gabapentin (Neurontin)	Initial: 100mg PO QHS MDD: determined by renal function; CrCl 60+: 3,600mg/day; CrCl 30-59: 1,400mg/day; CrCl 15-29ml/min: 700mg/day; CrCl 15ml/min: 300mg/day; CrCl < 15ml/min: (CrCl / 15) x 300mg	Capsule: 100mg, 300mg, 400mg Tablet: 600mg, 800mg	• Effective in 85% of patients with stage 4-5 CKD • May also benefit neuropathic pain • Sedation and dizziness are common adverse effects	Y
Pregabalin (Lyrica)	Initial: 25mg PO QHS MDD: determined by renal function; CrCl 30-60: 300mg/day; CrCl 15-30: 150mg/day; CrCl < 15: 75mg/day.	Capsule: 25mg, 50mg, 75mg, 100mg, 150mg, 200mg , 225mg, 300mg Oral solution: 20mg/ml	• Second-line therapy if gabapentin not tolerated • Effective in 85% of patients with stage 4-5 CKD • May also benefit neuropathy • Sedation and dizziness are common adverse effects • Expensive	Y
OTHER				
Calamine (Caladryl)	Initial: apply to affect are as often as needed MDD: n/a	Lotion: 8%	• Employed as an astringent, protectant and soothing agent • Most commonly used for contact dermatitis, sunburn, insect bites and other minor irritations	-
Camphor and Menthol (Sarna)	Initial: Apply topically to affected area several times daily	Lotion: 0.5% camphor, 0.5% menthol	• Over the counter • Avoid applying to broken skin	-
Doxepin (Sinequan)	Initial: 10-75mg QHS MDD: 300mg/day	Capsule: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg Oral solution: 10mg/ml	• Tricyclic antidepressant • Potent H1 and H2 histamine receptor antagonist • Low doses effective for treatment of pruritus	Y

References

- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 750-60.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 307-310.
- Davis, M. et al., Mirtazapine for Pruritus, Journal of Pain and Symptom Management, 2003: Vol. 25, No. 3, pp. 288-291.
- Fazio, S. et al. Pruritus: Etiology and patient evaluation, UpToDate, literature review current through Nov. 2015.
- Fazio, S. et al. Pruritus: Overview and management, UpToDate, literature review current through Nov. 2015.
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 141.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 870-2,934-9, 1287.
- Hicham, I. et al. Efficacy and safety of gabapentin for uremic pruritus and restless legs syndrome in conservatively managed patients with chronic kidney disease, Journal of Pain and Symptom Management, 2015, Vol. 49, No. 4.
- Keithi-Reddy, SR, et al, Uremic Pruritus, Kidney International (2007) 72, 373-377.
- Kobrin, S. et al. Uremic pruritus, UpToDate, literature review current through Nov. 2015.
- Kremer, A. et al. Pathogenesis and treatment of pruritus in cholestasis, Drugs, 2008; 68(15).
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Murtag, F. et al. Symptom management in patients with established renal failure managed without dialysis, EDTNA/ERCA journal, 2006, XXXII 2.
- O'Connor, N. et al. End-stage renal disease: symptom management and advance care planning, American Family Physician, 2012, Vol. 85, No. 7.
- Poupon, R. et al. Pruritus associated with cholestasis, UpToDate, literature review current through Nov. 2015.
- Rayner, H. et al. Uraemic pruritus: relief of itching by gabapentin and pregabalin, Nephron Clin Pract, 2012;122:75-9.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 204-205.
- Twycross, R. et al. Itch: scratching more than the surface, Q J Med, 2003; 96:7-26.
- Wsik, F, et al, Relief of uraemic pruritus after balneological therapy with a bath oil containing polidocanol (Balneum Hernial Plus, 1996, accessed online at http:informahealthcare.com/doi/abs/10.3109/09546639609089555

Mucous Membrane Dryness

DEFINITION

Mucous membrane dryness is a subjective, uncomfortable feeling of dryness associated with reduced mucus production or a change in the composition of saliva (mouth) or tear film (eyes).

CAUSES

GENERAL [1, 2, 3]

- Medications (most common cause of dry mucous membranes in elderly patients)
  - Antihypertensives
  - Alpha$_2$-agonists
  - Alpha-blockers
  - Anticholinergics
  - Antihistamines
  - Anti-Parkinson medications
  - Antipsychotics
  - Benzodiazepines
  - Beta-blockers
  - Chemotherapeutics
  - Diuretics
  - Medical marijuana/ dronabinol
  - Muscle relaxants
  - Sedatives
  - Tricyclic antidepressants
- Medical conditions
  - Inflammatory conditions (eg, sarcoidosis, amyloidosis)
  - Diabetes
  - Autoimmune conditions (eg, Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, scleroderma)
  - Cystic fibrosis
  - Psychological conditions (eg, anxiety, stress, fear)
  - Graft vs. host disease
  - Renal failure/dialysis
- Dehydration
- Other substances (eg, alcohol, caffeine, smoking tobacco)
- Exposure to wind, dust, smoke, allergens, or hot/dry environments

DRY MOUTH [1, 2]

- HIV-salivary gland disease
- Trauma or radiation therapy to head/neck (common; resulting from damage to salivary glands)

DRY EYES [4, 5]

- Conjunctivitis, blepharitis
- Structural abnormalities of the eyelid
- Dysfunction of lacrimal and meibomian glands responsible for secreting aqueous and oily tear film layers, respectively
- Reduced blinking (common in patients with Parkinson disease)

DRY NOSE [3, 6]

- Atrophic or allergic rhinitis
- Oxymetazoline nasal spray
- Use of a CPAP device or oxygen therapy
- Radiation therapy to head/neck

HOW TO RECOGNIZE SYMPTOMS

DRY MOUTH [2, 7]

- Complaints of dry mouth or "cotton mouth"
- Thirst that often worsens at night
- Pain / burning in mouth, tongue, or throat
- Difficulty speaking, swallowing, eating
- Dry, cracked lips
- Altered sense of taste
- Halitosis
- Altered saliva consistency (eg, stringy, rope-like, foamy)
- Changes in the appearance of the oral cavity including mucosa with redness or white spots (oral candidiasis), absence of saliva pooled in the floor of the mouth, or tooth decay

DRY EYES [4]

- Red eyes
- Gritty, burning, or foreign object sensation
- Light sensitivity

- Blurred vision
- Rheum (dried eye mucus)
- Difficult or painful blinking

DRY NOSE[3]

- Burning or itching sensation when breathing through nose
- Diminished sense of smell
- Epistaxis
- Visible blood/mucus crusting on inner nasal mucosa

CLINICAL INSIGHTS

GENERAL

- Identify and treat potentially reversible causes, when reasonable and in accordance with patient goals of care.
- Deprescribe offending medications/substances.
- Maintain adequate hydration.
- Avoid caffeine, alcohol, and tobacco products.
- Humidifiers may be useful in spaces where the patient spends a significant amount of time (eg, bedroom, living room).
- Saliva, tear and nasal mucus substitutes provide short-term relief and do not stimulate mucus production.

DRY MOUTH

- Non-pharmacologic interventions may be beneficial:[1]
  - » Frequent sips of water, ice chips, popsicles; moist, soft foods preferred over dry, crumbly foods (eg, cereals and crackers).
  - » Sugar free candy or gum may increase saliva production (if salivary glands remain functional)
  - » Avoid breathing in through the mouth if possible; a cold air humidifier may be beneficial for mouth breathers
  - » Emphasize good oral hygiene and denture care
- Symptomatic treatment typically involves stimulating saliva production and/or replacing it with an artificial substitute
- If saliva substitutes are used, attempt to choose a product with a neutral pH; acidic substitutes can worsen tooth decay.
- Dry mouth can hinder oral administration and reduce sublingual absorption of medications[8]
  - » Attempt to use easy to swallow medications, such as oral solutions/suspension
  - » Counsel patients to lubricate their mouth/throat with water prior to swallowing tablets/capsules and follow dose with a full glass of water
  - » When possible, moisten mouth with water or saliva substitute prior to administering SL tablet dosage forms to ensure absorption
- Cholinergic agonists can be tried for patients with salivary hypofunction who do not achieve symptomatic relief with saliva substitutes.
  - » GI adverse effects are common.
    - ° Pilocarpine and cevimelene can be taken with food to minimize dyspepsia and bloating.[7]
    - ° Separating bethanechol from meals can prevent nausea/vomiting.[9]
  - » Cevimelene may be less likely to cause cardiovascular effects due to higher affinity for M1 and M3 receptors (in lacrimal and salivary tissue) than for M2 receptors (in cardiac tissue).[7]
- Cholinergic agonists are not effective for patients with non-functional salivary glands; instead, saliva substitutes should be used.[8]

DRY EYES

- Non-pharmacologic interventions may be beneficial:
  - » Limit activities that reduce blink rate (ie, reading and screen time)
  - » Limit exposure to wind, dust, smoke, allergens
- Symptomatic treatment typically involves substituting tears with ophthalmic lubricants (also called 'artificial tears' or 'tear substitutes').
- Preservative-free tear substitutes are recommended for patients who develop inflammatory reactions to preservatives or require frequent administration (>4 times per day) for symptom control.[4] These are often marketed as single-use vials, typically cost more, and may be difficult for patients with arthritis to open.
- More viscous products (gels, ointments) require less frequent application.
- Warm compress application may improve secretions from meibomian glands.[4]

- Ophthalmic cyclosporine is widely used to treat dry eye, but a recent evidence review concluded that its effect on symptom improvement remains unclear.[4, 10]

DRY NOSE

- Symptomatic treatment typically involves applying saline-based or other topical moisturizers to the nasal mucosa and skin surrounding the nostrils.
- If the nasal mucosa is lined with thin and dry crusts, topical ointments, such as Vaseline, can be applied as a protective film to help reduce mechanical irritation and promote healing.[3]
- To reduce fire risk, petroleum-based products (eg, Vaseline) should not be used to moisturize the skin in or around the nose in patients receiving oxygen therapy; instead, oil-in-water creams or water-based products are recommended.[11]
- Oxymetazoline, a decongestant nasal spray, can cause mucosal dryness and inflammation and should not be used regularly or for prolonged periods (> 3 consecutive days).[9]

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
SALIVA SUBSTITUTES[7]				
Various (eg, carboxymethylcellulose, polyethylene glycol, sorbitol glycerin) (Biotene, Moi-Stir, Oasis)	Initial: Swish/Spray/ Dissolve/Rinse mouth as needed MDD: Not established	Gel, lozenge, powder, oral solution/spray: various	• Available OTC • First-line treatment for dry mouth symptoms • Safe and well-tolerated • Gels, sprays, and solutions can be applied to the inner lips, buccal mucosa, tongue, and hard palate • Sprays may be difficult for patients with arthritis to use	N/A

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CHOLINERGIC AGONISTS FOR DRY MOUTH [7, 9, 12, 13]				
Bethanechol (Urecholine)	Initial: 25mg PO TID MDD: Not established for this indication	Tablet: 5mg, 10mg, 25mg, 50mg	**Cholinergic Agonists** • Stimulate saliva production from hypoactive salivary glands • Caution in cardiac disease and COPD • Gradual titrations can improve tolerability • Adverse effect include diarrhea, nausea, vomiting, polyuria, and sweating **Pilocarpine** • May improve symptoms related to ocular, nasal, vaginal, and skin dryness • Ophthalmic solution can be given orally » 1 gtt of 2% sol. = 1mg » 1 gtt of 4% sol. = 2mg • More likely to cause sweating, flushing than cevimeline. • Almost immediate response if using for medication-induced symptoms, but may take 6-12 weeks for full effect if use related to radiation therapy • Caution if moderate hepatic impairment; avoid if severe impairment **Cevimeline** • More likely to cause GI side effects (eg, nausea, diarrhea) than pilocarpine • Beneficial effects may outlast pilocarpine due to longer half-life and receptor occupancy time • If no improvement after 6 weeks, may increase to 45mg TID **Bethanechol** • Off-label use • Give 1 hour before or 2 hours after meals to avoid nausea/vomiting • Adverse effects generally less severe compared to pilocarpine • Reduce dose if hypersalivation occurs • Contraindicated in asthma, cardiac disease, peptic ulcer disease, parkinsonism, intestinal or urinary obstruction	Y
Cevimeline (Evoxac)	Initial: 30mg* PO TID MDD: 135mg/day *If use is limited by adverse effects, reduced doses can be prepared by dissolving a fraction of capsule contents in water to create an oral solution; this can be swallowed or used as a mouth rinse (swish and spit) to minimize systemic absorption.	Capsule: 30mg		Y
Pilocarpine (Salagen)	Initial: 5mg PO QD-QID MDD: 30mg/day	Ophthalmic solution: 1%, 2%, 4% Tablet: 5mg, 7.5mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
TEAR SUBSTITUTES [4, 9, 14]				
Various (eg, polyethylene glycol, polyvinyl alcohol, petrolatum, mineral oil, glycerin, methylcellulose) (Refresh, Systane, GenTeal, etc.)	Gel/Solution: Instill 1-2 drops in each eye TID-QID PRN Ointment: Apply small amount (1/4 in.) to the inside of the eyelid TID-QID PRN MDD: Not established	Ophthalmic gel/ ointment/solution: various	• Available OTC • First-line treatment for dry eye symptoms • May take 3 to 4 weeks for significant improvement • Can be dosed every 30 to 60 minutes PRN • Switch to preservative-free formulation if used more often than QID; preservatives can damage ocular surface and worsen symptoms • Gels and ointments last longer than solutions; QHS administration recommended to minimize blurred vision and improve morning symptoms	N/A
MISCELLANEOUS AGENTS FOR DRY EYES [4, 9, 10, 14, 15]				
Cyclosporine (Restasis, Cequa)	Initial: Instill 1 drop in each eye BID (~12 hours apart) MDD (emulsion): 4 drops per eye/day MDD (solution): 2 drops per eye/day	Ophthalmic emulsion: 0.05% Ophthalmic solution: 0.09 %	• Delayed onset of approx. four weeks; may take up to 6 months for full effect • Separate from tear substitutes by 15 minutes • Adverse effects include eye pain or redness, burning sensation, blepharitis • Symptomatic improvement not observed with solution • Expensive	N/A
Lifitegrast (Xiidra)	Initial: Instill 1 drop in each eye Q12 hours MDD: 2 drops per eye/day	Ophthalmic solution: 5%	• Delayed onset of approx. two weeks; may take up to 12 weeks for full effect • Separate from tear substitutes by 15 minutes • Adverse effects include eye irritation, blurred vision, increased tear production, altered sense of taste • Expensive	N/A
NASAL MOISTURIZERS [9, 11]				
Sodium chloride (saline) (Ayr, Ocean Mist, etc.)	Administer to nostrils PRN MDD: Not established (may vary by dosage form)	Nasal gel, irrigation solution, rinse, solution: various	• Available OTC • Nasal irrigation more effective than sprays for removal of intranasal crusts, mucus, irritants, or allergens.	N/A
Water/glycerin (Ayr Gel)	Administer to nasal mucosa or to skin around and below nostrils PRN MDD: Not established	Nasal gel	• Available OTC • Preferred for moisturizing dry skin and mucous membranes related to oxygen therapy	N/A

References

1. Chai E, et al. Xerostomia and oral mucositis. In: Geriatric Palliative Care – A practical guide for clinicians. New York, NY: Oxford University Press; 2014:248-252.
2. Sreebny LM, et al. A reference guide to drugs and dry mouth – 2nd edition. Gerondontology. 1997;14(1):33-47.
3. Hildenbrand T, et al. Rhinitis sicca, dry nose and atrophic rhinitis: a review of the literature. Eur Arch Otorhinolaryngol. 2011;268:17-26.
4. Shtein R. Dry Eye Disease. In:UpToDate, Post TW (Ed), UptoDate, Waltham, MA. (Accessed/current through March 12, 2020)
5. Gilbard JP. The diagnosis and management of dry eyes. Otolaryngol Clin North Am. 2005;38(5):871-85.
6. DeShazo R, et al. Atrophic rhinosinusitis. In:UpToDate, Post TW (Ed), UptoDate, Waltham, MA. (Accessed/current through March 13, 2020)
7. Baer A. et al. Treatment of dry mouth and other non-ocular sicca symptoms in Sjögren's syndrome. In:UpToDate, Post TW (Ed), UptoDate, Waltham, MA. (Accessed/current through March 13, 2020)
8. Xerostomia: helping patients with dry mouth. The Oral Cancer Foundation. https://oralcancerfoundation.org/complications/xerostomia/. (Accessed March 12,2020)
9. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020.
10. DePaiva CS, et al. Topical cyclosporine A therapy for dry eye syndrome (Review). Cochrane Database Syst Rev. 2019;9:CD010051.
11. Bauters T, et al. Safety in the use of Vaseline during oxygen therapy: the pharmacist's perspective. International Journal of Clinical Pharmacy. 2016;38:1032-1034.
12. Twycross R, et al. Hospice and Palliative Care Formulary USA. 2nd ed. Nottingham, UK: Palliativedrugs.com Ltd; 2008:437.
13. Chambers MS, et al. Cevimeline for the treatment of postirradiation xerostomia in patients with head and neck cancer. Int. J. Radiation Oncology Biol. Phys. 2007;68(4):1102–1109.
14. Clinical Resource, Treatments for Dry Eyes. Pharmacist's Letter/Prescriber's Letter. March 2018.
15. Dastjerdi MH, et al. High-frequency topical cyclosporine 0.05% in the treatment of severe dry eye refractory to twice-daily regimen. Cornea. 2009;28(10):1091-1096.

Muscle Spasm & Spasticity

DEFINITION

Muscle spasms (also referred to as muscle cramps) are involuntary contractions that can be observed during electromyographic examination that may cause pain/ discomfort.

Spasticity is a muscle tone disorder characterized by hyperactive tonic stretch reflexes thought to arise from an imbalance of excitatory and inhibitory inputs at the level of the spinal cord often seen after injury to descending motor pathways.

CAUSES

- Neurological
  - » Neurological diseases such as Multiple Sclerosis, ALS
  - » Stroke
  - » Spinal cord/ head injury
  - » Nerve damage/inflammation
  - » Cancer (nerve/muscle invasion)
  - » Cerebral palsy
  - » Muscular dystrophies
- Nutritional
  - » Electrolyte abnormalities (eg, hypomagnesemia, hypokalemia)
  - » Dehydration
  - » Vitamin deficiency
- Physical
  - » Limited mobility
  - » Poor circulation
- Medication-induced
  - » Opioid accumulation/toxicity (myoclonus)
  - » Diuretics (via dehydration, electrolyte loss)
  - » Statins (muscle ache as adverse effect)

HOW TO RECOGNIZE SYMPTOM

- May be intermittent and/or induced/worsened with movement or postural changes
- Muscle spasm: complaints of diffuse aches / cramps that cause muscle pain and may interfere with functional ability and are associated with conditions such as tension headaches, back or neck pain and fibromyalgia
- There are two types of spasticity:
  - » Tonic spasticity – stiffness and rigidity with exaggerated reflexes
  - » Phasic spasticity – complaints of cramps, spasms and/or clonus

CLINICAL INSIGHTS

- Underlying causes should be sought out and addressed if possible
  - » Myoclonus can be induced by opioid metabolite accumulation (commonly with morphine or codeine).
  - » If opioid metabolite accumulation is not suspected or if opioid rotation is unsuccessful, benzodiazepines are typically effective treatments for myoclonus.
- Consider anti-inflammatory or opioid medications if symptoms are complicated by pain and inflammation
- A distinction should be made between muscle spasm and spasticity, which almost never occurs outside of the setting of brain or spinal cord disease or injury.
  - » For spasticity, an anti-spastic medication should be used, such as baclofen, tizanidine, diazepam, or less commonly, dantrolene.
  - » Other muscle relaxants (such as cyclobenzaprine and methocarbamol) are less likely to be effective for spasticity.
  - » Spasticity is most often a chronic condition, whereas muscle spasms are often transient.
- Sedation commonly occurs with muscle relaxant use; use caution with other CNS depressants due to additive effects.
- Muscle relaxants are poorly tolerated by elderly patients due to anticholinergic effects, sedation and risk of falls.
- Abrupt withdrawal of muscle relaxants may cause withdrawal symptoms; recommend gradual tapering if discontinuing.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTI-SPASTIC AGENTS				
Baclofen (Lioresal)	Initial: 5mg PO TID MDD: 80mg/day	Tablet: 10mg, 20mg	• Causes more motor weakness than tizanidine • Expensive	Y
Dantrolene (Dantrium)	Initial: 25mg PO QD x 7 days, then 25mg TID x 7 days, then doubled Q week or until symptom response MDD: 400mg/day	Capsule: 25mg, 50mg, 100mg	• Black-box warning: hepatotoxicity • Contraindicated if liver disease • Some patients may not respond at lower doses. Each dose titrations should be evaluated over a 7-day period. If no further efficacy despite titration, return to previous dose.	Y
Diazepam (Valium)	Initial: 2-5mg PO TID-QID PRN MDD: 40mg/day	Oral solution: 5mg/5ml, 5mg/ml Solution for injection: 5mg/ml Tablet: 2mg, 5mg, 10mg	• Very long half-life, use with caution in geriatric patients and consider dosing Q12-24 hours in this population • May worsen delirium/cognition in patients with dementia • Benzodiazepine of choice for muscle spasm/ spasticity • Contraindicated if severe liver disease	Y
Levetiracetam (Keppra)	Initial: 500mg PO BID MDD: 3,000mg/day	Oral solution: 100mg/ml Solution for injection: 100mg/ml Tablet: 250mg, 500mg, 750mg, 1,000mg Tablet (ER): 500mg, 750mg	• Case series of 20 motor neuron disease patients with cramping spasticity suggested possible efficacy • May cause behavioral problems, including: aggression, agitation, anger and emotional lability • Reduce dose if any level of renal impairment • Expensive	N
Tizanidine (Zanaflex)	Initial: 2mg PO TID MDD: 36mg/day	Capsule: 2mg, 4mg, 6mg Tablet: 2mg, 4mg	• Use with caution and reduce dose in patients with severe renal impairment • Titrate to efficacy as tolerated by 2-4mg per dose not more often than every 1-4 days • May cause orthostatic hypotension • Give consistently with food or on empty stomach • Causes more dry mouth than baclofen • Tablets are more cost-effective than capsules • Expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
SKELETAL MUSCLE RELAXANTS				
Carisoprodol (Soma)	Initial: 350mg PO TID-QID PRN MDD: 1,400mg/day	Tablet: 250mg, 350mg	• Associated with addiction and abuse • Not first line therapy • 250mg tablets are brand only and expensive	Y
Chlorzoxazone (Parafon Forte, Lorzone)	Initial: 250-500mg PO TID-QID MDD: 3,000mg/day	Tablet: 375mg, 500mg, 750mg	• May cause harmless discoloration of urine (red, orange)	Y
Cyclobenzaprine (Flexeril)	Initial (IR): 5mg PO TID PRN (5mg QD if elderly) Initial (ER): 15mg PO QD MDD: 30mg/day	Capsule (ER)*: 15mg, 30mg Tablet: 5mg, 7.5mg, 10mg	• Strongly anticholinergic (similar structure to amitriptyline); use caution in elderly or patients with cardiac disease. • 5mg and 10mg doses are similarly effective, but higher dose is associated with more adverse effects • Avoid use if severe liver disease • ER capsules and 7.5mg IR tablets are expensive	Y/N*
Metaxolone (Skelaxin)	Initial: 800mg PO TID-QID MDD: 3,200mg/day	Tablet: 400mg, 800mg	• Give on an empty stomach • Contraindicated if severe renal or hepatic impairment • Expensive	Y
Methocarbamol (Robaxin)	Initial (PO): 1,500mg QID x 2-3 days, then decrease to 1,000mg QID or 1,500mg TID Initial (inj.): 1,000mg IM/IV x 1 dose; may repeat Q8 hours x 3 days max MDD (PO): 8,000mg/day MDD (inj.): 3,000mg/day	Solution for injection: 100mg/ml Tablet: 500mg, 750mg	• May cause harmless discoloration of urine (back, blue, green) • Seizures have been reported with IV administration	Y
Orphenadrine (Norflex)	Initial (PO): 100mg BID Initial (inj.): 60mg IM/IV BID MDD: same as initial	Solution for injection: 30mg/ml Tablet (ER): 100mg	• Generally not recommended for use in elderly patients • Strongly anticholinergic (similar in structure to diphenhydramine)	N

References

- Abrams, G. et al. Chronic complications of spinal cord injury and disease, UpToDate, literature review current through Nov. 2015.
- Andersen, P. et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) – revised report of an EFNS task force, European Journal of Neurology, 2012, Vol. 19, 360-375.
- Bedlack, R. et al. Open-label pilot trial of levetiracetam for cramps and spasticity in patients with motor neuron disease, Amyotrophic Lateral Sclerosis, 2009; 10: 210-215
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp.405, 914.
- Consumer reports Health.org Best Buy Drugs – Evaluating Prescription Drugs used to Treat Muscle Spasms and Spasticity: The Muscle Relaxants – Comparing Effectiveness, Safety and Price
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 147.
- Galvez-Jimenez, N. et al. Symptom-based management of amyotrophic lateral sclerosis, UpToDate, literature review current through Nov. 2015.
- Gordon, P. et al. Amyotrophic lateral sclerosis: an update for 2013 – clinical features, pathophysiology, management and therapeutic trials, Aging and Disease, Vol. 4, No. 5, 295-310.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 1270, 1275.
- Isaac, Z. Treatment of neck pain, UpToDate, literature review current through Nov. 2015.
- Jenkins, T. et al. The evidence for symptomatic treatments in amyotrophic lateral sclerosis, Current opinion in Neurology, Vol. 27, No. 5, Oct. 2014.
- Knight, C. et al. Treatment of acute low back pain, UpToDate, literature review current through Nov. 2015.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Meleger, A. Muscle Relaxants and Antispasticity Agents, Physical Medicine and Rehabilitation Clinics of North America, 17 (2006) 401-413.
- Miller, RG, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review), Neurology, Vol.73 pp.1227-1233, 2009.
- Olek, M. et al. Symptom management of multiple sclerosis in adults, UpToDate, literature review current through Nov. 2015.
- Simmons, Z. Management strategies for patients with amyotrophic lateral sclerosis from diagnosis to death, The Neurologist, Vol. 11, No.5, Sept.2005.

DEFINITION

Nausea:

- An unpleasant and uneasy feeling and inclination to vomit; does not always lead to vomiting

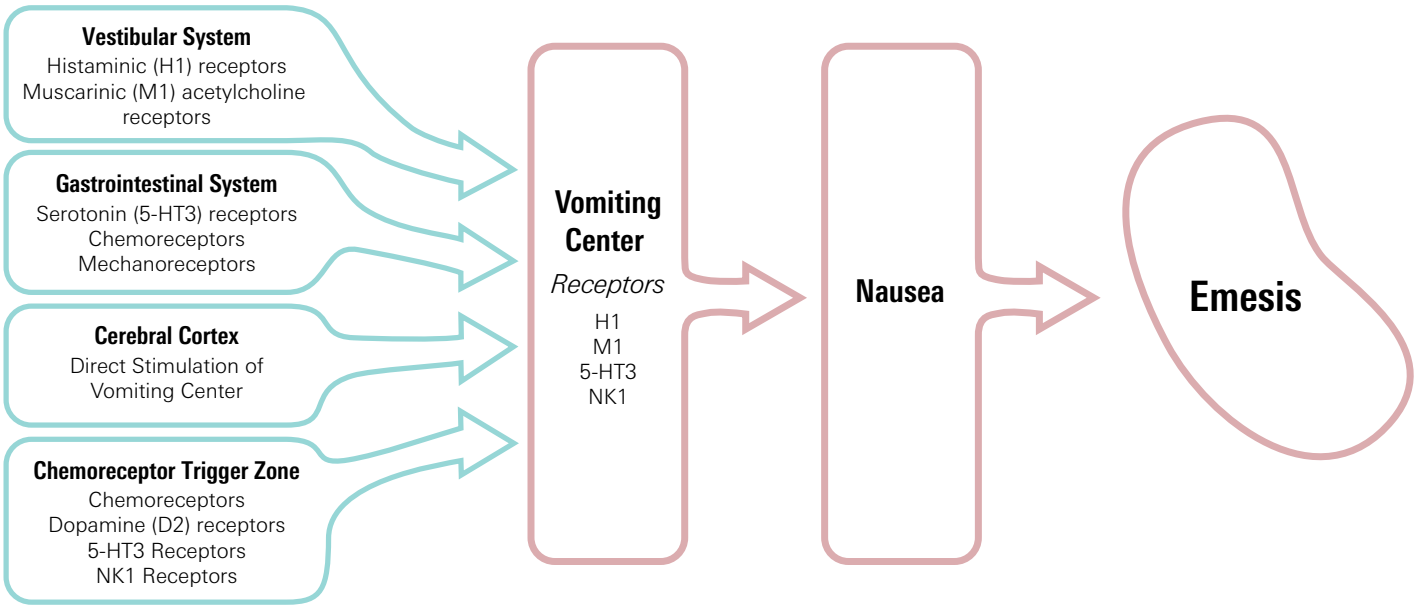
Vomiting:

- Voluntary or involuntary emptying to stomach contents through the esophagus and mouth.
- The vomiting center is located in the medulla and receives information from four major areas of the brain and body – the cerebral cortex, the chemoreceptor trigger zone, the GI tract, and the vestibular nerve.
- Upon stimulation of these areas, nausea and vomiting are mediated by the release of dopamine, histamine, acetylcholine, and serotonin.

CAUSES

- A common acronym to remember causes is "A VOMIT"
  - » Anxiety/Anticipatory
  - » Vestibular
  - » Obstructive
  - » Medications/Metabolites
  - » Infection/Inflammation
  - » Toxins
- Vestibular Nerve
  - » Stimulants: Motion and labyrinth disorders
  - » Receptors: Cholinergic, histaminic
  - » Examples:
    - ° Dizziness, vertigo, motion sickness
    - ° Meniere's disease
    - ° Vestibular neuritis
    - ° Inner ear disease or infection
    - ° Neurotoxin (alcohol)

FIGURE 1: NAUSEA AND VOMITING RECEPTOR PROFILES, MECHANISMS, AND PATHOPHYSIOLOGY



- Gastrointestinal Tract
  - » Stimulants: stasis, obstruction, mucosal injury, local toxins/drugs
  - » Receptors: Cholinergic, histaminic, 5-HT3
  - » Examples:
    - ° Medications
      - › NSAIDs, iron, alcohol, antibiotics, antifungals, digoxin, anticonvulsants, antidepressants, phenothiazines, anticholinergics
    - ° Visceral Causes
    - ° Stomach
      - › Gastritis, gastroparesis, peptic ulcer disease, peritoneal cancer
      - › Food poisoning, overeating, tube feedings
    - ° Colon:
      - › Bowel obstruction, pseudo-obstruction, constipation, Crohn's disease, ischemic bowel
    - ° Pancreas
      - › Pancreatic cancer, pancreatitis
    - ° Liver:
      - › Hepatitis, stretched liver capsule, ascites
    - ° Nervous system diseases that cause dysmotility
      - › Parkinson disease, Multiple sclerosis, ALS, autonomic dysfunction
    - ° Other:
      - › Appendicitis, chloecystitis, excessive pulmonary secretions, urethral distention
- Chemoreceptor Trigger Zone:
  - » Stimulants: Drugs (opioids, digoxin, antibiotics, chemotherapy), metabolic products, bacterial toxins
  - » Receptors: Dopamine-2 (D2), serotonin (5-HT3)
  - » Examples:
    - ° Medications – opioid induced
    - ° Metabolic disturbances (eg, renal or hepatic failure, tumor products)
    - ° Electrolyte disturbances (eg, hyponatremia, hypercalcemia)
    - ° Diabetic ketoacidosis
    - ° Radiation
    - ° Sepsis
- Cerebral Cortex
  - » Stimulants: Sensory input, anxiety, increased intracranial pressure
  - » Receptor: Directly stimulates receptor in the vomiting center
  - » Examples:
    - ° Stress
    - ° Strong smells or tastes
    - ° Anxiety or anticipation of nausea-inducing events
    - ° Uncontrolled pain
    - ° CNS Injury
      - › Tumor / metastases, hemorrhage, infection
    - ° Migraine
- Other Conditions:
  - » Hyperthyroidism
  - » Myocardial infarction

HOW TO RECOGNIZE SYMPTOM

- Direct observation or patient reports nausea symptom
- Vomiting may be preceded by spasms of diaphragm and abdominal muscles or retching
- Symptoms may be accompanied by pallor, cold sweats, salivation, tachycardia, diarrhea, upset stomach, and anorexia
- Patients may experience weakness, anorexia, dehydration, and electrolyte loss following emesis

CLINICAL INSIGHTS

- Nausea and vomiting triggers may induce more than one pathway in the brain
  - » Opioids can trigger the vestibular nerve, cause GI stasis, and trigger the chemoreceptor zone
  - » Opioids may sensitize the vestibular nerve, causing movement-induced nausea that is more likely to affect ambulatory patients. Anticholinergics and antihistamines are preferred agents in these cases due to the predominant involvement of acetylcholine and histamine.
  - » Serotonin (5-HT3) antagonists and dopamine (D2) antagonists block the release of neurotransmitters from the chemoreceptor trigger zone that may be stimulated by opioids nausea may be the result

of gastroparesis and delayed gastric emptying caused by opioids

- Opioid induced nausea is an inclination to vomit that may begin within a few doses of starting an opioid medication.
  - » Initiation or escalation of opioid dose is associated with nausea or vomiting
  - » Nausea and vomiting related to opioid administration is usually dose-related and temporary, often subsiding within 2 – 3 days of initiation
  - » When titrating an opioid regimen, slow titration can help reduce nausea
  - » Can be treated with dopamine antagonists such as haloperidol
- Anxiety or anticipation of nausea-inducing events
  - » Benzodiazepines are used to help control anxiety, but have minimal antiemetic properties
- Approaching Therapy:
  - » Nausea can be reversible and irreversible
  - » Attempt to identify cause or trigger of nausea and neurotransmitter involved in stimulating pathway
  - » Mechanical model: treat based on underlying cause of nausea and target the neurotransmitters that are responsible for stimulating the vomiting center
  - » Empirical model: treat based on provider preference/experience if precipitating cause cannot be found
  - » Potentially reversible causes of nausea and vomiting should be assessed to help guide therapy (listed below are some examples)
    - ° Tumor, increased intracranial pressure – steroid
    - ° Uncontrolled pain – opioids/pain medications
    - ° Vestibular disease/motion sickness – antihistamines/anticholinergics
    - ° Infection – antibiotics, bismuth sulfate (for GI infections)
    - ° Medication toxicity – reduce/discontinue medication
    - ° Constipation – laxatives
    - ° Gastroparesis/delayed gastric emptying – prokinetic agent
    - ° Excessive pulmonary secretions – anticholinergics
    - ° GI irritation from medications – PPI, H2 Blocker, bismuth sulfate
  - » Consider adjusting doses or intervals of medications that may cause nausea and vomiting.
  - » Consider scheduling antiemetic for the first few days following opioid initiation/dose increase
- Non-pharmacological therapy
  - » Attempt to remove offending agents
  - » Maintain small meals with easy to digest foods (eg, "BRAT" diet: bananas, rice, apple sauce, toast)
  - » If possible, avoid triggers (strong smells, bad taste)
  - » Use relaxation techniques to prevent nausea induced anxiety
  - » Inhaling vapors from 70% isopropyl alcohol swabs / pads significantly reduced nausea in a trial of otherwise healthy patients; similar results have been observed in case reports of palliative care patients. Aromatherapy with peppermint and ginger may also be beneficial.

TABLE 1 – PHARMACOLOGICAL AGENTS USE BASED ON INDICATION AND AFFECTED PATHWAYS

MEDICATION CLASS	INDICATIONS/ CAUSES	AFFECTED PATHWAYS
Dopamine Antagonists	• Medication • Metabolic related nausea and vomiting	• Chemoreceptor trigger zone
Antihistamine	• Vestibular causes	• Vestibular system • Vomiting center
5-HT3 Antagonist/ NK1 Antagonist	• Useful for chemotherapy induced, post-operative, and post-radiation therapy	• Chemoreceptor trigger zone • Gastrointestinal system • Vomiting center
Corticosteroid	• Useful for increased intracranial pressure, to decrease tumor size, has antiemetic properties	• Cerebral cortex
Anticholinergic Agent	• Vestibular causes	• Gastrointestinal system • Vestibular system • Vomiting center
Prokinetic Agent	• Nausea and gastric stasis from various causes	• Gastrointestinal system

Refractory nausea and vomiting:

- Review likely cause of nausea to determine if alternate medication is useful
- Combination regimens may be required from different classes
- For frequent symptoms may consider scheduled doses for optimal effect

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DOPAMINE ANTAGONISTS				
Chlorpromazine (Thorazine)	Initial: 10-25mg PO Q4-6H routine or PRN MDD: 150mg/day	Injection: 25mg/ml Tablet: 10mg, 25mg, 50mg, 100mg, 200mg	• 4:1 oral to IV potency • Side Effects: sedation, orthostasis, extrapyramidal symptoms • Suppositories can be compounded • Tablets, injection expensive	Y
Haloperidol (Haldol)	Initial: 0.5-1mg PO/PR/ SQ/ IM/IV/SL Q12h or q4-6h routine or PRN MDD: Not established for this indication	Oral solution: 2mg/ml Solution for injection (lactate): 5mg/ml Tablet: 0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg	• Potent dopamine antagonist • 2:1 oral to IV potency • Low sedation index compared to other antipsychotics • Rarely require higher doses than 1 to 2mg BID to TID • Extrapyramidal symptoms are rare at low doses	Y
Olanzapine (Zyprexa)	Initial: 2.5-10mg QD MDD: 20mg/day	Oral disintegrating tablet (ODT) (Zydis formulation): 5mg, 10mg, 15mg, 20mg Tablet: 2.5mg, 5mg, 10mg, 15mg, 20mg	• Block multiple receptors in the nausea/vomiting pathway (dopamine, serotonin, histamine, anticholinergic) • Useful for refractory nausea and vomiting • SE: somnolence, dry mouth, constipation, hyperglycemia • Expensive	Y
Prochlorperazine (Compazine)	Initial: PO: 5-10mg TID-QID routine or PRN PR: 25mg Q12h routine or PRN IM: 5-10mg Q3-4H routine or PRN (edisylate) MDD (PO): 40mg/day MDD (PR): 50mg/day	Oral solution: 5mg/5ml Solution for injection: 5mg/ml Suppository: 25mg Tablet: 5mg, 10mg	• Side effects: sedation, extrapyramidal symptoms • The rectal maximum daily dose is occasionally exceeded in the hospice setting • Suppositories expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIHISTAMINES				
Dimenhydrinate (Dramamine)	Initial: 50mg Q4-6H routine or PRN MDD: 400mg/day	Chewable tablet: 50mg Solution for injection: 50mg/ml Tablet: 50mg	• Side effects: tachycardia, excitation, restlessness	Y
Diphenhydramine (Benadryl)	Initial: 25-50mg PO/ IV/SQ q6h routine or PRN MDD: 400mg/day	Capsule: 25mg Oral solution: 12.5mg/5ml Tablet: 25mg, 50mg	• Sedating • Avoid in elderly or demented patients due to anticholinergic adverse effects	Y
Hydroxyzine (Visaril, Atarat)	Initial: 10-25mg PO/IM q6h routine or PRN MDD: Not established for this indication	Capsule (Pamoate): 25mg, 50mg, 100mg Oral solution: 10mg/5ml, 25mg/5ml Solution for injection: 25mg/ml, 50mg/ml Tablet (HCl): 10mg, 25mg, 50mg, 100mg	• Antihistamine with anxiolytic properties • Sedating • IV/SQ administration not recommended • Active ingredient available as different salt forms, pamoate and hydrochloride	Y
Meclizine (Antivert, Bonine, Dramamine Less Drowsy)	Initial: 12.5-50mg PO q6h routine or PRN MDD: 100mg/day	Chewable tablet: 25mg Tablet: 12.5mg, 25mg, 50mg	• Sedating • Chewable tablets may be administered with or without water, or swallowed whole with water • Onset of action is 1 hour and effects may last from 8-24 hours	Y
Promethazine (Phenergan)	Initial: 12.5-25mg PO/ PR/IV/IM q4-6h routine or PRN MDD: 100mg/day	Oral solution: 6.25mg/5ml Solution for injection: 12.5mg/ml, 25mg/ml, 50mg/ml Suppository: 12.5mg, 25mg, 50mg Tablet: 12.5mg, 25mg, 50mg	• Antihistamine and dopamine antagonist • Sedating • Suppositories expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
SEROTONIN TYPE 3 ANTAGONISTS (5-HT3) AND SUBSTANCE P/NK1 ANTAGONISTS				
Aprepitant (Emend)	Initial: 125mg on day 1, then 80mg daily on days 2-3 MDD: N/A	Capsule: 40mg, 80mg, 125mg, 80mg, 125mg	• Useful for chemotherapy induced nausea • Not commonly used as first line therapy in the hospice setting • Can be used in conjunction with 5-HT3 antagonists/corticosteroids • Expensive	Y
Granisetron (Ganisol)	Initial (PO/IV/SQ): 0.5-1mg QD-BID or 2mg QD Initial (topical) 1 patch topically changed weekly MDD (PO/IV/SQ): 2mg/day MDD (topical): 1 patch topically changed weekly	Patch: 3.1mg/24 hours Solution (oral): 2mg/10ml Solution for injection: 0.1mg/ml, 1mg/ml Tablet: 1mg	• Not commonly used as first line therapy in the hospice setting • Useful for chemotherapy induced nausea; severe or refractory nausea. • If not effective in 3 days, may consider alternate therapy. • May cause headache, constipation, diarrhea • Expensive	Y
Ondansetron (Zofran)	Initial: 4-8mg PO/IV/SQ q8h routine or PRN MDD: 24mg/day	Oral disintegrating tablet (ODT): 4mg, 8mg Oral solution: 4mg/5ml Solution for injection: 4mg/2ml Tablet: 4mg, 8mg, 24mg	• Not commonly used as first line therapy in the hospice setting • Useful for chemotherapy induced nausea; severe or refractory nausea. • If not effective in 3 days, may consider alternate therapy. • May cause headache, constipation, diarrhea • Expensive	Y
CORTICOSTEROIDS				
Dexamethasone (Decadron)	Initial: 4mg PO/PR/SQ/IV QD-QID MDD: 48mg/day	Oral solution: 0.5mg/5ml, 1mg/ml Solution for injection: 4mg/ml, 10mg/ml Tablet: 0.25mg, 0.5mg, 0.75mg, 1mg, 1.5mg, 2mg, 4mg, 6mg	• First line therapy for nausea due to increased intracranial pressure • Give last dose by 2pm if suspected steroid induced insomnia	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICHOLINERGIC AGENTS				
Glycopyrrolate (Robinul)	Initial: 1-2mg PO q4-6h 0.2mg SQ/IV q4-6h MDD: Not established	Solution for injection: 0.2mg/ml Tablet: 1mg, 2mg	• Can be used symptom control of malignant bowel obstruction • Does not cross blood-brain barrier, therefore, less likely to cause delirium than other anticholinergics	Y
Hyoscyamine (Levsin)	Initial: 0.125-0.25mg PO/SL q4h routine or PRN 0.25-0.5mg IV/SQ q4h routine or PRN MDD: 1.5mg/day	Elixir: 0.125mg/5ml Oral disintegrating tablet (ODT): 0.125mg Oral solution: 0.125mg/ml Solution for injection: 0.5mg/ml Tablet: 0.125mg Tablet (ER): 0.375mg	• Antacid may interfere with absorption	Y
Scopolamine (Transderm Scop)	Initial: 1.5mg patch Apply 1 patch topically Q3 days routine or PRN MDD (topical): 1 patch q72h	Transdermal patch: 1.5mg	• Does not work immediately; 6-8 hours for onset of action • Apply on clean, dry, hairless skin behind ear • Wash hands before and after application • Anecdotally, the maximum daily dose is occasionally exceeded in the hospice setting • Expensive	-
PROKINETIC AGENTS				
Erythromycin (EES, Eryped)	Initial: 250mg PO TID MDD: 1,500mg/day	Oral Suspension: 200mg/5ml Tablets: 250mg, 500mg	• Consider for N/V caused by delayed gastric emptying • Can be given with food to decrease GI upset, do NOT give with milk or acidic beverages • Use oral base preparations (not enteric coated)	N
Metoclopramide (Reglan)	Initial: 5-10mg PO/ PR/IV/SQ TID-QID (before meals and at bedtime) routine or PRN MDD: 40mg/day	Injection: 5mg/ml Oral Solution: 5mg/5ml Tablets: 5mg, 10mg	• Start with 5mg TID to QID for elderly patients • Avoid use in Parkinson disease patients	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER				
Dronabinol (Marinol)	Initial: 2.5mg BID MDD: 20mg/day	Capsule: 2.5mg, 5mg, 10mg	• Synthetic cannabinoid • Indicated for chemotherapy induced nausea-vomiting • Reserve use for refractory nausea and vomiting • Expensive	N
Mirtazapine (Remeron)	Initial: 15-45mg Q HS MDD: 45mg/day	Solutabs: 15mg, 30mg, 45mg Tablets: 7.5mg, 15mg, 30mg, 45mg	• Acts on 5-HT3 receptor and can be useful for refractory nausea/vomiting • May be useful for patients who may also have depression, anorexia, itching, anxiety, pain	Y
Trimethobenzamide (Tigan)	Initial (PO): 300mg PO TID-QID routine or PRN Initial (IM): 200mg IM TID-QID routine or PRN MDD (PO): 1,200mg/day MDD (IM): 800mg/day	Capsule: 300mg Injection: 100mg/ml	• Antiemetic of choice in Parkinson patients • Requires renal dosing • Expensive	Y

References

- April MD, et al. Aromatherapy versus oral ondansetron for antiemetic therapy among adult emergency department patients: A randomized controlled trial. Annals of emergency medicine. 2018;72(2):184-193.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 337, 390-1, 546-53, 882.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 271-274.
- Corona AGDL, et al. Olfactory distraction for management of nausea in palliative care patients. 2021. American Journal of Hospice & Palliative Medicine. May 2021.
- Critchley, P. et al. Efficacy of Haloperidol in the Treatment of Nausea and Vomiting in the Palliative Patient: A Systematic Review, Journal of Pain and Symptom Management, Vol. 22 No. 2, 2001 pp. 631-34.
- Davis, M. et al. A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation, Journal of Pain and Symptom Management, Vol.39 No.4, 2010, pp. 756-767.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3p: Nausea-vomiting, accessed online Nov. 2015 at: http://www.cancer.gov/resources-for/hp/education/epeco/self-study/module-3/module-3p-pdf
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 114.
- Hallenbeck, J. The causes of nausea and vomiting (VOMIT), Fast Fact #5 CAPC, accessed online at: https://www.capc.org/fast-facts/5-causes-nausea-and-vomiting-vomit/
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 686,801-7,810,1034-5,1476-7
- Hardy, J. et al. The Efficacy of Haloperidol in the management of Nausea and Vomiting in Patients with Cancer, Journal of Pain and Symptom Management, Vol. 40 No. 1, 2010 pp. 111-15.
- Kaneishi, K. et al. Olanzapine for the Relief of Nausea in Patients with Advanced Cancer and Incomplete Bowel Obstruction, Journal of Pain and Symptom Management, Vol.44 No.4, 2011.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Longstreth, G. et al. Approach to the adult with nausea and vomiting, UpToDate, literature review current through Nov. 2015.
- Peroutka, S. et al. Antiemetics: neurotransmitter receptor binding predicts therapeutic actions, The Lancet, March 20th, 1982, pp. 658-9.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 157.
- Ross DD, Alexander CS. Management of Common Symptoms in Terminally Ill Patients: Part 1. Fatigue, Anorexia, Cachexia, Nausea and Vomiting. AAFP, 2001: 64(5) 807-814.
- Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 308-319,329-336.

Oral Mucositis / Stomatitis

DEFINITION

Diffuse inflammatory, erosive ulcerative condition of the mucous membranes of the mouth

CAUSES

- Radiation/ chemotherapy
- Cancer (eg, Kaposi sarcoma, non-Hodgkin's lymphoma)
- Trauma due to localized injury (eg, poorly fitting dentures)
- Infection
  - » Viral (eg, herpes simplex virus)
  - » Bacterial (eg, gingivitis)
  - » Fungal (eg, candida and other species)
- Stress
- Poor oral hygiene
- Medications:
  - » Sulfa drugs
  - » Steroids
  - » Antibiotics
- Predisposing factors:
  - » Dry mouth
  - » Nutritional deficiencies
  - » Hematopoietic disorders

HOW TO RECOGNIZE SYMPTOM

- Red, shiny or swollen areas inside the mouth or on the gums
- Sores in the mouth, on the gums or under the tongue
- White exudates, white film or yellow film anywhere in the mouth
- Dry, brittle, easily torn or bleeding mucous membranes in the mouth
- Oral pain especially when eating or drinking
- Difficult or uncomfortable swallowing
- Altered taste
- Halitosis (bad breath)
- Decreased appetite

CLINICAL INSIGHTS

- Chemotherapy induced mucositis typically heals by itself in 2-4 weeks when no infection is present
- Radiation induced mucositis typically takes 6-8 weeks to heal (usually dependent upon the length of the course of radiation)
- Pain management improves quality of life and allows patient to communicate and eat normally
- Dental and oral hygiene should be comprehensive (eg, brushing of teeth, flossing of gingival tissues)
- Mucous membranes and lips should be kept moist; consider artificial saliva or lip balm
- Severe pain may need to be managed by systemic analgesics
- Secondary microbial colonization of lesions can lead to local or systemic infection
  - » Drug treatment is based on the colonizing organism
  - » Consider initiation of antibiotic treatment if bacterial infection is present/suspected
  - » Consider initiation of antifungal treatment if funcal infection is present/suspected
  - » Acyclovir may be useful in preventing recurrent herpetic lesions in patients that are immunocompromised.
- Local application of ice/cold may provide relief
- Avoid alcohol-containing mouthwashes because they can cause pain/discomfort, xerostomia, and delay wound healing.
- Oral protectants or coating agents can be used to provide a protective barrier to minimize mouth pain and allow the patient to eat and drink
- Sucralfate suspension has historically been used with the intent of providing a protective coating for the oral mucosa, but a recent evidence review concluded that studies clearly demonstrated a lack of benefit in the prevention or treatment of oral mucositis.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
LOCAL ANESTHETICS				
Benzocaine gel (Orajel)	Initial: Apply to affected area up to QID PRN MDD: 4 applications per day	Dental gel: 6.3%, 7.5%, 10%, 20%	• Anesthetic to provide short term pain relief • Indicated for aphthous stomatitis (ulcers)	-
Maalox/ Benadryl/ Lidocaine (Miracle mouthwash compound)	Initial: Swish and expectorate 5-15ml up to QID PRN MDD: 60ml/day	Compounded solutions may contain varied combinations of ingredients listed	• Mucosal protectant/anti-inflammatory/ anesthetic to reduce pain, inflammation and facilitate healing • Anesthetic to provide short term pain relief • Effects last longer when not eating or drinking at least 30 min after application • Limited evidence to support use and efficacy	-
Lidocaine (Xylocaine)	Initial: 5ml swish and expectorate PRN every 4-6 hr MDD: 8 doses/day	Viscous solution: 2%	• Anesthetic to provide short term pain relief • Helpful to facilitate eating and oral care • Effects last longer when not drinking or eating at least 30 min after application	-
ANALGESIC RINSE				
Morphine (Roxanol)	Initial: rinse mouth with 15ml of 0.2% morphine solution for 2 min. then spit out every 3-4 hours PRN MDD: same as initial for this indication	Compounded solution of 0.2% morphine rinse can be made by adding 30ml of 20mg/ml morphine oral solution to 270ml of water for total volume of 300ml	• Contraindicated if unable to spit out contents of rinse • Test patient prior to using by giving 15ml of water to rinse with, then measure the recovered amount. If patient unable to spit out 90% or more (13.5ml) of the test solution, do not use. • Not absorbed systemically to appreciable extent if used correctly	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ORAL ANTISEPTIC				
Chlorhexidine (Peridex, Paroex, Periogard)	Initial: Swish and expectorate 15ml for 30 sec BID following tooth brushing MDD: Same as initial	Oral rinse: 0.12%	• Do not swallow • Used for secondary infection	-
ANTI-INFLAMMATORY				
Triamcinolone acetonide (Oralone)	Initial: press a small amount (~1/4 inch) to lesion until thin film develops MDD: not established	Oral paste: 0.1%	• Oral paste is indicated for aphthous stomatitis • Use only enough to coat lesion and do not rub in	-
CAUTERIZING				
Sulfonated phenolics and sulfuric acid (Debacterol)	Topical: Apply 1 coated applicator swab to ulcer for 5-10 seconds MDD: 1 treatment to each ulcer	Topical solution: 50/30%	• Treatment for individual small aphthous stomatitis • Chemical cauterization of ulcer leads to rapid relief of pain after initial intense pain during application • Not suitable for friable mucous membranes, large areas, or mucositis • Limited evidence to support use and efficacy	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MISCELLANEOUS				
Doxepin (Sinequan)	Initial: 2.5ml of 10mg/ml oral solution diluted with 2.5ml of water rinsed for 1 minute then spit out Q 4 hours PRN	Oral solution: 10mg/ml	• Diminishes pain due to oral mucositis • Tricyclic antidepressant with anesthetic and analgesic properties when administered topically • May cause stinging, burning or unpleasant taste • Despite spitting out, may cause drowsiness	-
Ketamine (Ketalar)	Initial (mouthwash): Swish 20mg ketamine in 5ml saline or artificial saliva for 30-60 seconds, then spit out. Repeat QID and Q3-4 hours PRN MDD: not established for this indication	Solution for injection: 10mg/ml, 50mg/ml, 100mg/ml	• Off-label use • Rapid onset of effect in 15min or less is typical • Can be compounded to improve taste • Adverse effects are uncommon because dose is not swallowed • May gargle, but should not swallow solution • Refrain from eating or drinking for at least 30min before or after use • May continue any other topical mucositis treatments if needed, but recommend separating administration by at least 1 hour before or after ketamine rinse	-

References

- AAHPM, Unipac 4: Managing non-pain symptoms.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 566, 882.
- Cerchietti, L. et al. Effect of Topical Morphine for Mucositis-Associated Pain following Concomitant Chemoradiotherapy for Head and Neck Carcinoma, Cancer, Vol. 95 No. 10, 2002.
- Cerchietti, L. et al. Potential Utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study, Pain, 105 (2003) 265-273.
- DynaMed – stomatitis treatment
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3o: Mucositis, accessed online Nov. 2015 at: http://www.cancer.gov/resources-for/hp/education/epeco/self-study/module-3/module-3o-pdf
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 516,529,607,609,819,957,1005-8.
- Leenstra, James, et al., Doxepin Rinse Versus Placebo in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Head and Neck Radiotherapy With or Without Chemotherapy: A Phase III, Randomized, Double-Blind Trial, Journal of Oncology,32(15):1571-7, 2014 May 20.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Medline Plus website. www.nlm.nih.gov/medlineplus/ency/patientinstructions/00047.htm. Accessed Sept 3, 2015
- Negrin, R. et al. Oral toxicity associated with chemotherapy, UpToDate, literature review current through Nov. 2015.
- Saunders, D. et al. Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients, Supportive Care in Cancer, 21(11):3191-207, 2013 Nov.
- Shillingburg, A. Treatment of severe mucositis pain with oral ketamine mouthwash, Support Care Cancer, 2017; published online 11 Feb 2017.
- Slatkin, N. et al. Topical ketamine in the treatment of mucositis pain, Pain Medicine, 2003;4(3):298-303.
- The Oral Cancer Foundation website. http://oralcancerfoundation.org/complications/mucositis.php. Accessed Sept 1, 2015

Neuropathic Pain

DEFINITION

Neuropathic pain is pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system.

CAUSES

- Cancer, metastatic spread or cancer treatments (eg, chemotherapy, radiation)
- Diabetes (diabetic neuropathy)
- Shingles (post-herpetic neuralgia)
- Stroke (central poststroke pain)
- Neuromuscular disease (eg, ALS, multiple sclerosis)
- Uremia
- HIV neuropathy
- Peripheral nerve injury
- Amputation (phantom limb syndrome)
- Post-surgical pain syndromes
- Fracture
- Spinal cord injury or metastases
- Trigeminal neuralgia
- Glossopharyngeal neuralgia
- Lumbar radiculopathy (sciatica)
- Carpal tunnel syndrome
- Chronic alcoholism with malnutrition (particularly B-vitamins)
- Complex regional pain syndromes

HOW TO RECOGNIZE SYMPTOM

- Pain can be described as sharp, burning, stabbing, shooting, tingling, or like electrical shocks
- Paradoxical numbness is often described accompanying pain
- Pain may develop immediately after nerve injury, or may develop several months later
- Hypersensitivity to heat or cold
- Pain elicited as a response to a non-nociceptive stimulus such as light touch

CLINICAL INSIGHTS

- Pharmacotherapy can improve quality of life in many patients with neuropathic pain, but complete pain remission with drug therapy is uncommon.
  - » Medications for neuropathic pain typically offer satisfactory pain relief in ≤ 50% of patients
  - » Adverse effects are common
  - » Typically, agents used for neuropathic pain have numbers needed to treat (NNTs) of between 2 to 6 patients.
  - » A common reason for treatment failure is inadequate dose titration
    - ° If a treatment is partially effective, titrate to highest tolerated dose that provides pain relief without adverse effects
- Most medications used are not indicated for treatment of neuropathic pain and are used off-label
- Patients may require combination therapy with multiple agents for neuropathic pain. In these cases, agents with differing mechanisms of action should be chosen.
  - » If monotherapy is only partially effective, in some patients combination therapy may provide greater pain relief with fewer adverse effects than escalating a single drug regimen
  - » Exception: tramadol is typically avoided with SNRIs and TCAs due to the increased risk of adverse effects due to serotonin syndrome
- There is currently no treatment algorithm that should be applied universally to all patients in the hospice setting.
- Pain descriptors can be useful to guide choice of pharmacotherapy:
  - » Continuous burning or tingling, pain on light touch may respond better to tricyclic antidepressants or serotonin norepinephrine reuptake inhibitors
  - » Shooting, stabbing pain may respond better to antiepileptics, lidocaine, baclofen or tramadol
- Choice of pharmacotherapy should consider comorbid conditions, potential for adverse effects, drug-drug interactions, drug-disease interactions and medication cost. Attempt to choose an agent with multi-symptom benefit. For example,

  - » TCAs may improve symptoms of depression, insomnia and Sialorrhea
  - » SNRIs may improve symptoms of anxiety and/or depression
  - » Ketamine may improve symptoms of depression
  - » Methadone and tramadol may improve somatic nociceptive pain
  - » Antiepileptics may reduce seizure frequency
- Typical first line agents include antidepressants with both serotonin and norepinephrine reuptake inhibition (eg, TCAs and SNRIs) or gabapentin/pregabalin
- Of the available TCAs, nortriptyline and desipramine are preferred because of equal efficacy and fewer adverse effects than other TCAs
  - » Onset of analgesia with tricyclic antidepressants (TCAs) is about 7 days. For partial response, titrate to efficacy or as tolerated by 25mg per week over 6-8 weeks
  - » 2 weeks of therapy at the maximum tolerated dose should be evaluated to determine efficacy
- Of the available SNRIs, duloxetine and venlafaxine are preferred
  - » SNRIs are more expensive than TCAs
- Opioids may be considered for neuropathic pain, especially if multimodal pain with nociceptive component.
  - » Generally not considered first line therapy for chronic non-cancer pain
  - » Associated with more adverse effects than TCAs or gabapentin/pregabalin
  - » May be beneficial on a PRN basis for episodic exacerbations
  - » May be more useful in certain types of neuropathic pain than others
    - ° More effective – painful polyneuropathy, postherpetic neuralgia, phantom limb pain and mixed neuropathic pain
    - ° Less effective – central post-stroke pain
- Methadone and tramadol are synthetic opioids with additional unique properties that make them more beneficial than other opioids in treating neuropathic pain.
  - » Patients with chronic mixed pain of nociceptive and neuropathic types should be evaluated as candidates for methadone conversion
- Carbamazepine and oxcarbazepine are drugs of choice for trigeminal neuralgia

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIDEPRESSANTS THAT BLOCK SEROTONIN AND NOREPINEPHRINE (TCAS / SNRIS)				
Amitriptyline (Elavil)	Initial: 10-25mg PO QHS MDD: 300mg/day	Tablet: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	• Tricyclic antidepressant • Most sedating / anticholinergic TCA	Y
Desipramine (Norpramin)	Initial: 10-25mg PO QHS MDD: 300mg/day	Tablet: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	• Tricyclic antidepressant • Least anticholinergic TCA • Elderly max dose 150mg/day	Y
Duloxetine (Cymbalta)	Initial: 30mg PO daily MDD: 60mg/day	Capsule: 20mg, 30mg, 60mg	• Drug of choice for chemotherapy-induced neuropathic pain • SNRI • Titrate to 60mg/day after 1 week if tolerated • Nausea is the primary adverse effect, but can be minimized by starting at doses < 60mg per day. • Doses greater than 60mg/day offer no additional benefit, but are associated with increased adverse effects • Consider lower starting doses if tolerability a concern or if renal impairment • Contraindicated if hepatic impairment • Contents of capsule may sprinkled into soft food or fluid and swallowed immediately • Associated with significant withdrawal syndrome if missed doses	N
Nortriptyline (Pamelor)	Initial: 10-25mg PO daily MDD: 150mg/day	Capsule: 10mg, 25mg, 50mg, 75mg Oral solution: 10mg/5ml	• Tricyclic antidepressant • Least anticholinergic TCA	Y
Venlafaxine (Effexor)	Initial (IR): 37.5mg PO BID Initial (ER): 37.5-75mg PO QD MDD: 225mg/day	Capsule (ER)*: 37.5mg, 75mg, 150mg Tablet: 25mg, 37.5mg, 50mg, 75mg, 100mg Tablet (ER)*: 37.5mg, 75mg, 150mg, 225mg	• SNRI • Titrate by 75mg / week to efficacy or as tolerated • Generally requires a 2-4 week titration to an effective dose • Avoid or use with caution in patients with cardiovascular disease • Nausea is a common adverse effect • Do not crush or open extended release capsules • Associated with significant withdrawal syndrome if missed doses	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIEPILEPTICS				
Carbamazepine (Tegretol)	Initial (IR Tabs, ER tabs, ER caps): 100mg BID Initial (Suspension): 50mg QID MDD (all forms): 1,600mg/day	Capsules (ER)*: 100mg, 200mg, 300mg Suspension: 100mg/5ml Tablets (Chewable): 100mg Tablets (ER)*: 200mg, 400mg Tablets (IR): 200mg	• Do not crush ER tabs/ caps • Drug of choice for trigeminal neuralgia • Commonly involved in significant drug-drug interactions (enzyme inducer)	Y/N*
Clonazepam (Klonopin)	Initial: 0.25-0.5mg TID MDD: 4mg/day	Oral Disintegrating Tablet (ODT): 0.25mg, 0.5mg, 1mg, 2mg Tablet: 0.5mg, 1mg, 2mg	• Limited evidence to support efficacy for neuropathic pain • Consider in patients with comorbid anxiety • Consider orally disintegrating tabs if patient cannot swallow • May worsen agitation/ behaviors in dementia patients	Y
Divalproex (Depakote)	Initial: 250mg PO HS x7d, then 500mg PO HS	Sprinkle capsule (DR): 125mg Tablet (DR): 125mg, 250mg, 500mg Tablet (ER): 250mg, 500mg	• Can be dosed once daily for pain • Can be compounded into rectal suppositories • Drug level monitoring should be considered for seizures only • Sprinkle capsules can be opened, but contents should not be crushed	N
Gabapentin (Neurontin)	Initial: 100-300mg PO TID or 100-300mg QHS if concerns of adverse effects MDD: 3,600mg/day	Capsule: 100mg, 300mg, 400mg Oral solution: 250mg/5ml Tablet: 100mg, 300mg, 400mg, 600mg, 800mg	• Wide effective dose range • Titrate to TID dosing for maximum efficacy unless contraindicated • Commonly causes sedation and dizziness; use caution in ambulatory patients. Start at low doses and titrate as tolerated. • Dose adjust if renal impairment • Adequate trial can require 2 months or more • No clinically significant drug interactions *(Continued on next page)*	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIEPILEPTICS (CONTINUED)				
Oxcarbazepine (Trileptal)	Initial (IR): 300mg PO BID Initial (ER): 600mg PO QD MDD (all forms): 2,400mg/day	Oral suspension: 300mg/5ml Tablet: 150mg, 300mg, 600mg Tablet (ER)*: 150mg, 300mg, 600mg	• Drug of choice for trigeminal neuralgia • Typical onset of effect is within 48 hours for trigeminal neuralgia • Fewer drug interactions compared to carbamazepine • ER tablets are brand only and expensive	Y/N*
Lacosamide (Vimpat)	Initial: 50mg PO BID MDD: 400mg/day	Oral solution: 20mg/ml Tablet: 50mg, 100mg, 150mg, 200mg	• Titrate by 100mg weekly to efficacy; typical effective dose studied was 400mg/day • Off label use • Clinical trials do not consistently demonstrate efficacy • Dose adjust if renal or hepatic impairment	Y
Lamotrigine (Lamictal)	Initial: see initial titration schedule and dosing in chapter on seizure prevention and control MDD: not established for this indication; 200mg/day was studied for central poststroke pain; 400mg/day was studied for painful diabetic neuropathy	Chewable tablet: 5mg, 25mg Tablet: 25mg, 100mg, 150mg, 200mg Tablet (ER)*: 25mg, 50mg, 100mg, 200mg, 250mg, 300mg	• See additional comments in chapter on seizure prevention and control • Studies demonstrated efficacy in relieving central post-stroke pain and painful diabetic polyneuropathy • Studies failed to show efficacy in mixed neuropathic pain or pain in multiple sclerosis or due to polyneuropathy	Y/N*
Pregabalin (Lyrica)	Initial: 50mg PO TID or 75mg BID MDD: Typically 300mg/day; higher doses have been used, but are associated with more adverse effects without improved efficacy.	Capsule: 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg	• Commonly causes sedation and dizziness; use caution in ambulatory patients. Start at low dose and titrate slowly. • May provide analgesia more rapidly than gabapentin • Dose adjust if renal impairment • No clinically significant drug interactions • Expensive	Y
Valproic Acid (Depakene)	Initial: 250mg PO HS x7d, then 500mg PO HS	Capsule: 250mg Syrup: 250mg/5ml	• Can be dosed once daily for pain • Can be compounded into rectal suppositories • Drug level monitoring should be considered for seizures only	N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
SYNTHETIC OPIOID AGONISTS WITH ADDITIONAL MECHANISMS				
Methadone (Dolophine, Methadose)	Individualized dosing	Oral solution: 5mg/5ml, 10mg/5ml, 10mg/ml Tablet: 5mg, 10mg	• Inexpensive • Additional mechanisms include inhibition of serotonin/norepinephrine reuptake and NMDA receptor antagonist • Use with extreme caution. Peak respiratory depressant effects occur after and last longer than peak analgesic effects • Should not be used on a PRN basis • Excellent for nociceptive and neuropathic pain • Preferred opioid for patients with renal or hepatic impairment • May increase risk of hypoglycemia; when initiating at doses ≥ 40mg/day, consider blood glucose monitoring • Call clinical pharmacist for dosage recommendations	Y
Tramadol (Ultram, Conzip, Synaprin)	Initial: 50mg PO QD-BID MDD: 400mg/day (300mg/day if > 75yo)	Capsule (ER)*: 100mg, 200mg, 300mg Oral suspension: 10mg/ml Tablet: 50mg, 100mg Tablet (ER)*: 100mg, 200mg, 300mg	• Additional mechanisms are inhibition of serotonin/norepinephrine reuptake • Rapid onset of analgesia • Titrate every 3-7 days until efficacy or as tolerated • Contraindicated if seizure disorder • Increases risk of serotonin syndrome if used with antidepressants • Dose adjust if renal impairment • Ineffective if severe hepatic impairment • May increase risk of hypoglycemia • Extended release formulations and suspension are expensive	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER				
Baclofen (Lioresal)	Initial: 5-10mg PO TID (may start as low a 10mg QD, then titrate by 10mg QOD) MDD: 80mg/day	Tablet: 10mg, 20mg	• Antispasticity agent • Can be used for neuropathic pain due to trigeminal neuralgia either alone, or as adjunct therapy to carbamazepine or oxcarbazepine • Up to 75% of patients with trigeminal neuralgia report pain relief	Y
Capsaicin (Zostrix, Trixaicin)	Initial: Apply small amount to painful area 3-4 times daily MDD: 4 applications/ day	Cream: 0.025%, 0.075%, 0.25% Gel: 0.025%, 0.05%, 0.075%, Lotion: 0.035% Patch: 8% Stick: 0.075%	• Substance P depleter • Excellent safety profile • Wash hands after use • Do not apply to mucus membrane areas • May take up to several weeks for full effect; avoid in patients with a limited prognosis of weeks or less • Patch is expensive	-
Clonidine (Catapres)	Initial (PO): 0.2mg PO QD Initial (transdermal): 0.1mg patch topically changed every 7 days MDD (oral): 2.4mg/day MDD (transdermal): 0.6mg/24 hours	Patch: 0.1mg/24hr, 0.2mg/24hr, 0.3mg/24hr Tablet: 0.1mg, 0.2mg, 0.3mg	• Antihypertensive that stimulates alpha-2 receptors in the CNS • Off label use studied in patients with post-herpetic neuralgia • Monitor for hypotension • Do not discontinue suddenly as rebound hypertension can occur • For transdermal patch, apply to the most painful lesion • Compounded topical gel may be effective • Transdermal system is expensive	Y
Dronabinol (Marinol)	Initial: 2.5-5mg PO BID MDD: 20mg/day	Capsule: 2.5mg, 5mg, 10mg	• Excellent safety profile • Studied in patients w/ neuropathic pain due to multiple sclerosis • Commonly causes drowsiness • Expensive	N
Lidocaine (Xylocaine, Lidoderm)	Initial: 1 patch up to 12 hours/day MDD: 3 patches	Cream: 3%, 4%, 5% Ointment: 5% Patch: 5% Topical jelly: 2%	• Local anesthetic • Rapid onset • Excellent safety profile • Consider if pain is well-localized, such as focal peripheral neuropathy due to postherpetic neuralgia with allodynia • May cut patches • Patch, ointment and 3% cream expensive *(Continued on next page)*	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER (CONTINUED)				
Ketamine (Ketalar)	Initial (PO): 10-25mg PO TID-QID. May titrate as rapidly as 5mg per dose or 20mg per day. Additional doses can be given as needed at 1/10th to 1/6th of the total daily scheduled amount although as-needed use is not well-studied. Initial (SQ infusion): 100mg over 24 hours Initial (IV infusion): 0.6mg/kg over 4 hours Note: for infusions, consider administering daily for two 5-day infusion periods, separated by a 2-day ketamine-free interval MDD (PO): typically 200mg/day, although daily doses as high as 900mg/day have been reported. MDD (SQ infusion): 500mg/day MDD (IV infusion): 100mg over 4 hours	Injection: 10mg/ml, 50mg/ml, 100mg/ml	• Not first line therapy • Has been studied in nearly every type of pain, but with conflicting results • Consider when: other agents have been tried and failed or were only partially effective and in patients with multimodal pain with a neuropathic component • Disassociative anesthetic used at subanesthetic doses for analgesia • NMDA receptor antagonism thought to provide benefits in reducing opioid tolerance and improved neuropathic pain. Because of mechanistic overlap with methadone (both block NMDA), patients maintained on methadone may be less likely to benefit with ketamine use. • May allow decreased opioid requirements. Consider an empiric opioid dose reduction of 25% if commencing with ketamine for pain. If respiratory depression occurs with concomitant use of ketamine and opioids, reduce opioid dose as ketamine is unlikely to cause significant respiratory depression • Avoid in patients with schizophrenia (and similar disorders), those with raised intracranial pressure and those with conditions where increased BP/ HR would be hazardous • May cause both psychiatric (eg, euphoria, psychosis, delirium) and somatic (eg, hypertension, tachycardia, hypersalivation, raised intracranial pressure, GI distress, and cystitis) side effects. Daily doses higher than 400mg/day are significantly more likely to cause adverse effects. Approximately half of patients will experience adverse effects when using ketamine at analgesic doses, although they do not always lead to discontinuation. • In some cases, adverse effects can be mitigated with other medications (eg, haloperidol for delirium, labetalol for HTN/tachycardia)	-

References

- Aleksandrova, L. Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism, J Psych Neurosci, 2017.
- Bennett, M. et al. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review, Pain, 153(2012)359-365.
- Bial, A. et al. Assessment and Treatment of Physical Pain Associated with Life-Limiting Illness, AAHPM Hospice and Palliative Care Training for Physicians – A Self-Study Program – UNIPAC 3, 2008.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 368-9, 403-9, 468, 475, 482-92.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 159.
- Dworkin, R. Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update, Mayo Clin Proc, 2010; 85(3)(suppl):S3-S14.
- Eisenberg, E. et al. Lamotrigine reduces painful diabetic neuropathy, Neurology, 2001(57).
- Facts and comparisons off-label monographs – accessed via Lexicomp.
- Faskowitz, A. et al. Methadone-Induced Hypoglycemia, Cellular and Molecular Biology, 2013, 33:537-42.
- Fine, P. The Hospice Companion, 2nd ed, Oxford University Press, 2012.
- Fine, P. The Hospice Companion, 2nd ed., Ketamine protocol, appendix 3, pp. 174.
- Finnerup, N. et al. Algorithm for neuropathic pain treatment: an evidence based proposal, Pain, 118(2005)289-305.
- Flory, J. et al. Methadone Use and the Risk of Hypoglycemia for Inpatients with Cancer Pain, Journal of Pain and Symptom Management, 2015, article in press.
- Fournier, J. et al. Tramadol Use and the Risk of Hospitalization for Hypoglycemia in Patients with Noncancer Pain, JAMA Internal Medicine, 2015, Vol. 175, No. 2, pp. 186-93.
- Gordon, D. et al. Treatment of pain crisis at end of life from severe lower extremity venous outflow obstruction with hyperalgesia and allodynia, J Pain, 2002;3(3):244-8.
- Gould, et al. Ketamine mechanism of action: Separating the wheat from the chaff, Neuropsychopharmacology Reviews, (2017)42:368-9.
- Hurley, R. et al. Neuropathic pain: treatment guidelines and updates, Current Opinion in Anesthesiology, Vol.26, No. 5 2013.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 594-5,601,607,626-35,715-20,735.
- Ketamine, Lexicomp: Mechanism of action.
- Jefferies, K. Treatment of Neuropathic Pain, Semin Neurol., 2010; 30(4):425-432.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Majithia, N. et al. New practical approaches to chemotherapy-induced neuropathic pain: Prevention, assessment, and treatment, Oncology, Nov 2016: 1020.
- Marchetti, F. et al. Efficacy and safety of oral ketamine for the relief of intractable chronic pain: A retrospective 5-year study of 51 patients, Eur J Pain; 2014.
- Markman, J. et al. Neuropathic pain, Merck Manuals, accessed online Nov. 2015 at: http://www.merckmanuals.com/professional/neurologic-disorders/pain/neuropathic-pain
- O'Connor, A. et al. Treatment of Neuropathic Pain: An Overview of Recent Guidelines, The American Journal of Medicine, Vol. 122, No. 10A, Oct. 2009.
- Prommer, E. Ketamine for pain: an update of uses in palliative care, J Pall Med, 2012;15(4):474.
- Quibell, R. et al. Therapeutic Reviews: Ketamine, Journal of Pain and Symptom Mgmt, 2015;50(2):268-78.
- Rigo, FK, et al. Management of neuropathic chronic pain with methadone combined with ketamine: A randomized, double blind, active-controlled clinical trial, Pain Physician, 2017;20:207-15.
- Rosenquist, E. et al. Overview of the treatment of chronic pain, UpToDate, literature review current through Nov. 2015.
- Svendsen, K. et al. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial, British Medical Journal, 329:253, 2004.
- Torrance, N. Neuropathic pain in the community: more under-treated than refractory? Pain, 154(2013)690-99.
- Vestergaard, K. et al. Lamotrigine for central poststroke pain, Neurology, 2001(56)

Nociceptive Pain - Bone

DEFINITION

Aching or discomfort originating in bone tissue

CAUSES

- Leukemia, osteosarcoma
- Bone metastases; most commonly associated with cancer of the:
  - » prostate, breast, lung, kidney, bladder and multiple myeloma
- Cancer-induced bone resorption
- Hypercalcemia
- Spinal cord compression
- Fractures/breaks
- Viral disease
- Gouty arthritis
- Osteoporosis

HOW TO RECOGNIZE SYMPTOM

- Diagnosis of malignant bone pain is usually be made by history and physical exam. Bone pain syndrome includes background, spontaneous and incident pain.
- Described as a dull, deep, throbbing pain that cannot be easily localized
- Intermittent or continuous pain that increases with change in position or weight bearing, such as walking or standing

CLINICAL INSIGHTS

- Not all bone metastases are painful
- Bone pain can be:
  - » mild or severe
  - » intermittent or constant
  - » rapidly progressing
- Bone pain can occur as a side effect of:
  - » Biologic response modifiers (filgrastim, pegfilgastrim, sargramostim)
  - » Hormonal therapy (leuprolide, goserelin, tamoxifen, anastrazole, exemastane, raloxifene, letrozole)
  - » Chemotherapy
  - » Bisphosphonates (eg, alendronate, risendronate)
- Pain associated with bone metastases can be due to direct invasion of a bone, secondary pathologic fracture, damage to adjacent structures or bone marrow expansion (hematologic malignancies)
- Can exacerbate symptoms such as insomnia, fatigue, loss of appetite or depression
- Bone metastases commonly appear in the spine, pelvis, hip, base of skull and extremities
- Chest wall pain can be due to tumor infiltration of the ribs in patients with lung cancer
- NSAIDs in bone pain
  - » Clinical observations provide the base of support for the use of NSAID's in bone pain
  - » Choice of a specific agent is empiric
  - » Attention must be paid to comorbidities (especially gastric, cardiovascular, renal and hepatic disease) when prescribing these agents
  - » Risk for drug-induced adverse effect increases with a history of ulcer, age >60, increasing NSAID dose, concurrent use of steroids or anticoagulants
  - » Gastrointestinal side effect risk can be minimized by concurrent administration of a PPI or H2RA
- Corticosteroids in bone pain are effective agents for management of bone pain
  - » Extensive experience with corticosteroids suggest that they may be beneficial for bone pain but the results of randomized trials are inconclusive. A 2015 systematic review of six randomized trials found weak evidence for modestly less pain as compared to a control.
  - » While dexamethasone is usually preferred, no evidence exists that one corticosteroid is safer or more effective than another
- Opioids are also considered highly effective at treating bone pain, particularly when added to a NSAID or corticosteroid. No specific agent is preferred.
- Bone pain can be multifocal and often requires multiple analgesics / adjuvants for optimal control
  - » Bone pain and neuropathic pain may coexist (ex, tumor invasion of the spinal cord or cranial neuralgias)
- Opioid analgesia is often needed for spontaneous or incident pain flares but does not always require

adjustment to the background dose. Use caution when adjusting background (routine) dosing of opioids in response to multiple PRN doses to avoid opioid toxicity.

- Bisphosphonate infusions are sometimes associated with multifocal bone pain.
  - » Variable intensity and can be severe
  - » Typically occurs within 24 hours of infusion and lasts up to 3 days
  - » Usually self-limiting but analgesics may be required
- Non-pharmacologic treatment options include:
  - » Heat/cold
  - » Repositioning
  - » Acupuncture
  - » Massage
  - » Music therapy
  - » Reiki
- Radiation therapy (single or multiple fraction)
  - » Current guidelines from the American Society for Radiation Oncology supports single fraction therapy as to its convenience and cost effectiveness
  - » While treatment can be effective at any level of pain, early intervention provides for the highest quality of life and allows reduced analgesic use
  - » Partial pain relief reported in 60-80% of patients and complete pain relief reported in 15-58% of patients
- Radiopharmaceuticals can provide pain relief from bone metastases but choosing therapy is influenced by life expectancy, comorbidities and status of disease
  - » Generally used for diffuse skeletal metastases inadequately treated by analgesics or for hormone-insensitive disease
  - » Response rates vary based on primary disease, choice of radio nucleotide and dose administered
  - » Pain relief reported at 1-4 weeks after initiation of treatment and continues for 6-18 months
  - » Typically associated with a reduction in analgesic use
- Hormonal therapy, surgery (to stabilize the skeleton) and kyphoplasty are additional treatment options

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
STEROIDS				
Dexamethasone (Decadron)	Initial: 2-16mg PO/IV/ SQ QD-BID MDD: 40mg/day	Oral solution: 0.5mg/5ml, 1mg/ml Solution for injection: 4mg/ml, 10mg/ml Tablet: 0.25mg, 0.5mg, 0.75mg, 1mg, 1.5mg, 2mg, 4mg, 6mg	• Preferred over prednisone due to less sodium and water retention • Long half-life (duration of action 36-72 hours) • Highest relative anti-inflammatory activity • Relatively low mineralocorticoid effects • May cause GI upset; take with food or milk • Give last dose by 2pm to avoid steroid induced insomnia • Doses up to 1mg/kg/day have been reported • Use with caution in diabetics due to potential for blood glucose derangement • Caution in patients with recent GI bleed	Y
Methylprednisolone (Medrol)	Initial: 4-48mg PO daily MDD: 120mg/day	Tablet: 2mg, 4mg, 8mg, 16mg, 32mg	• May cause GI upset; take with food or milk • No mineralocorticoid effect • Use with caution in diabetics due to potential for blood glucose derangement • Caution in patients with recent GI bleed	Y
Prednisone (Orasone)	Initial: 5-20mg PO daily MDD: 80mg/day	Oral solution: 1mg/ml, 5mg/ml Tablet: 1mg, 2.5mg, 5mg, 10mg, 20mg, 50mg	• Use with caution in diabetics due to potential for blood glucose derangement • May cause GI upset; take with food or milk • Duration of action 12-36 hours • Caution in patients with recent GI bleed	Y

Nociceptive Pain - Bone

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)				
Celecoxib (Celebrex)	Initial: 100-200mg PO daily MDD: 400mg/day	Capsule: 100mg, 200mg, 400mg	• Caution in patients with sulfa allergy • Caution in patients with recent GI bleed • Capsules may be emptied into apple sauce • May cause GI upset; take with food or milk • Caution in patients with recent GI bleed	Y
Choline Magnesium Trisalicylate (Trilisate)	Initial: 500mg PO Q8 hours MDD: 4,000mg/day	Oral solution: 500mg/5ml Tablet: 500mg, 750mg, 1,000mg	• Do not use with salicylates or aspirin allergy • Less GI effects • May cause GI upset; take with food or milk • Caution in patients with recent GI bleed	Y
Ibuprofen (Advil, Motrin)	Initial: 200-400mg TID MDD: 3,200mg/day	Capsule: 200mg Chewable tablet: 100mg Oral suspension: 100mg/5ml, 40mg/ml Tablet: 200mg, 400mg, 600mg, 800mg	• May cause GI upset; take with food or milk • Caution in patients with recent GI bleed	Y
Naproxen Sodium (Naprosyn, Aleve)	Initial: 250-500mg PO BID MDD: 1,500mg/day	Tablet: 250mg, 375mg, 500mg Tablet (naproxen sodium): 220mg, 275mg, 550mg	• Long acting NSAID • 275mg naproxen sodium = 250mg naproxen • May be safer than other NSAIDs for patients with cardiac disease • May cause GI upset; take with food or milk • Caution in patients with recent GI bleed • OTC very inexpensive *(Continued on next page)*	N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) (CONTINUED)				
Salsalate (Disalcid)	Initial: 500mg PO Q12 hours MDD: 4,000mg/day	Tablet: 500mg, 750mg	• Onset of action takes 3 to 4 days • May cause GI upset; take with food or milk • Caution in patients with recent GI bleed	Y
Diclofenac Sodium (Voltaren)	Initial (DR): 25mg PO Q8 hours Initial (ER): 100mg PO QD MDD (all forms): 200mg/day	Tablet (DR): 25mg, 50mg, 75mg Tablet (ER): 100mg	• Can cause severe liver toxicity (highest risk among NSAIDs) • Discontinue if systemic manifestations of liver disease develop (eg, eosinophilia, rash, abdominal pain, diarrhea and dark urine) • May cause GI upset; take with food or milk • Caution in patients with recent GI bleed	N
Indomethacin (Indocin)	Initial (IR): 25mg PO q8h-q12h Initial (ER): 75mg PO QD MDD (all forms): 200mg/day	Capsule: 25mg, 50mg Capsule (ER): 75mg	• Only NSAID that can cross blood brain barrier; potential to cause CNS adverse effects • May cause GI upset; take with food or milk • Caution in patients with recent GI bleed	Y
Nabumetone (Relafen)	Initial: 1,000mg PO QD MDD: 2,000mg/day	Tablet: 500mg, 750mg	• Onset of action takes 4 to 6 days • May cause GI upset; take with food or milk • Caution in patients with recent GI bleed	Y
Sulindac (Clinoril)	Initial: 150mg PO BID MDD: 400mg/day	Tablet: 150mg, 200mg	• Potentially less renal toxic than other NSAIDs • May cause GI upset; take with food or milk • Caution in patients with recent GI bleed	Y

Nociceptive Pain - Bone

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BISPHOSPHONATES				
Pamidronate (Aredia)	Initial: 60-90mg IV over 90-120 min. q4 weeks MDD: 90mg/day	Solution for injection: 3mg/ml, 6mg/ml, 9mg/ml	• Solution must be diluted prior to administration • Requires SCr monitoring • May lose effectiveness over time	-
Zoledronate (Zometa)	Initial: 4mg IV over 15 minutes every 3-4 weeks MDD: same as initial	Solution for injection: 4mg/5ml	• Requires SCr monitoring • May lose effectiveness over time	-
PALLIATIVE RADIATION				
Samarium-153 lexidronam (Quadramet)	Initial: 1mCi/kg administered over 1 minute followed by a saline flush	Solution for injection: 1,850mbq/ml	• Some patients report pain flare within 72 hours of injection – usually mild and self-limiting • Radioactivity present in excreted urine for 12 hours following administration • Expensive	-
Strontium-89 (Metastron)	Initial: 148 megabecquerels (4 millicuries) or 1.5-2.2 megabecquerel (40-60 microcurie)/kg by slow IV injection over 1 to 2 mintues MDD: 2.2 megabecquerel/kg per dose	Solution for injection: 1mCi/ml	• Do not repeat injection more than once every 90 days • Expensive	-

References

- Agarwal, JP et al. Criteria for palliation of bone metastases – clinical applications. International Atomic Energy Agency. April 2007.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 493-504
- Clezrdin P et al. Potential anticancer properties of bisphosphonates: Insights from preclinical studies. Anticancer Agents Med Chem.2011 Aug 17.
- Fallon, Marie. "Cancer-induced Bone Pain." Oxford Textbook of Palliative Medicine. By Lesley A. Colvin. 4th ed. Oxford: Oxford UP, 2010. 638-53. Print.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 558,562,610-12,638-49,723-5.
- Hess G, Barlev A, Chung K, Hill J, and Fonseca E. Cost of palliative radiation to the bone for patients with bone metastases secondary to breast or prostate cancer. Radiation Oncolody 2012, 7:168. 1-7
- Ibrahim T, Farol, A, Metcatali L, Ricci M, and Amadori A. Metastatic bone disease in the era of bone-targeted therapy: clinical impact. Tumori. 2013 Jan-Feb;99(1):1-9
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Matzo, Marianne, and Deborah Witt. Sherman. "Bone Pain." Palliative Care Nursing: Quality Care to the End of Life. New York: Springer Pub., 2010. 204-07. Print.
- Metastatic Bone Disease. Amaerican Academy of Orthopaedic Surgeons. http://orthoinfo.aaos.org. October 2011. Online. Accessed 5/30/2013
- Portenoy, R. et al. Cancer pain management: Adjuvant analgesics (coanalgesics), UpToDate, literature review current through Nov. 2015.
- Shuling L et al. Estimated number of prevalent cases of metastatic bone disease in the US adult population. Clin Epidemiol. 2012;4: 87-93
- Talreja DB. Importance of antiresorptive therapies for patients with bone metastases from solid tumors. Cancer Management and Research 2012:4 287-297
- Tarumi, Yoko. "Bone Pain." Textbook of Palliative Medicine. London: Hodder Arnold, 2009. 493-504. Print.
- Working Group of the Clinical Practice Guideline for Palliative Care. Clinical Practice Guideline for Palliative Care. Madrid (Spain): Basque O" ce for Health Technology Assessment, Osteba; 2008

Nociceptive Pain - Tissue

DEFINITION

Pain is an unpleasant sensory and emotional experience for a patient. No definitive pathophysiological mechanism exists because pain is subjective in nature.

CAUSES

- Tissue damage / injury / trauma
- Cancer and cancer treatments
- Disease progression
- Chronic pancreatitis
- Functional bowel disorders
- Inflammatory disorders
- Ischemic heart disease
- Musculoskeletal disorders
- Sickle cell disease
- Infection
- Medication adverse effects (eg, statins)

HOW TO RECOGNIZE SYMPTOM

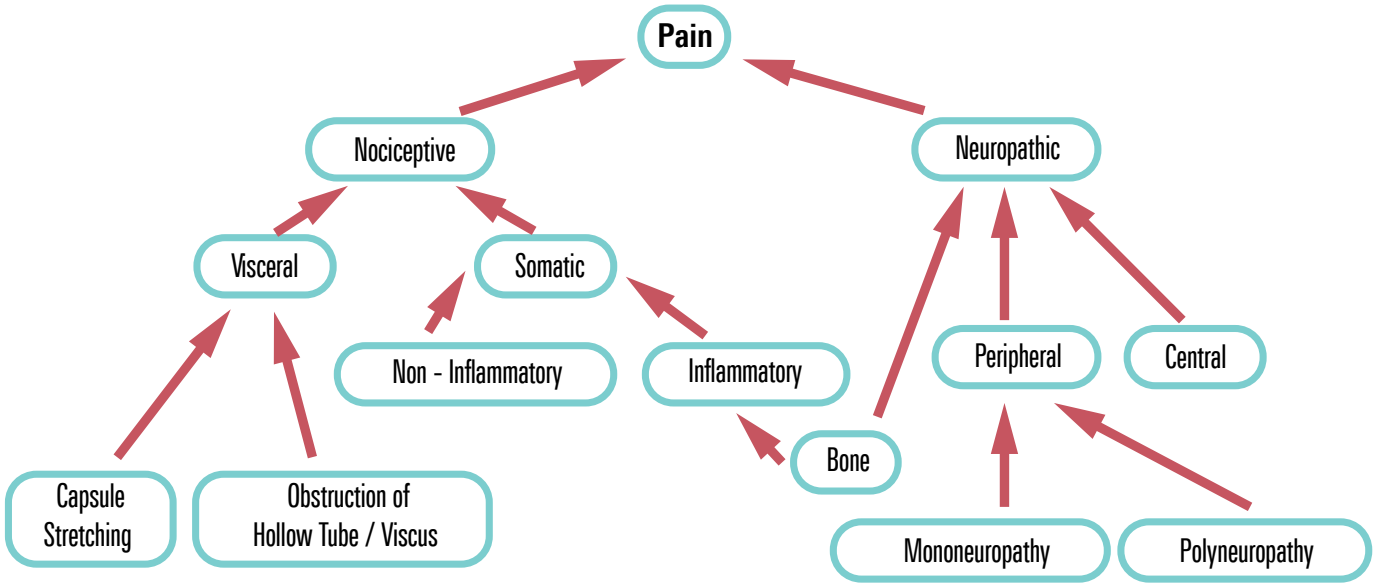
- Verbal
  - » Patient reporting pain
  - » Repeated calling out or crying
  - » Moaning
- Non-verbal signs and symptoms include:
  - » Facial grimacing
  - » Patient may appear tense or distressed
  - » Patient may appear rigid and may be striking out
  - » Patient may or may not be able to perform daily tasks
  - » Noisy labored breathing, long periods of hyperventilation
  - » Agitation
  - » Changes in behavior
- Different types of pain can present in different ways

CLINICAL INSIGHTS

- It is important to conduct a full assessment to determine an appropriate treatment plan
  - » Consider aggravating/alleviating factors, pain descriptors, radiation, duration
  - » Different types of pain exist and can be divided according to their pathophysiology (**Figure 1**). These respond to different treatment approaches.
    - ° Nociceptive (tissue) pain – results from tissue damage; intact neurons properly convey damage to CNS and pain is experienced. Can be either somatic or visceral.
      - › Treatment approaches: acetaminophen, NSAIDs, opioids
    - ° Neuropathic – see neuropathic pain chapter
    - ° Visceral – type of nociceptive pain that results from internal organs. Two types of visceral pain exist: those that involve the capsule surrounding organs or those obstructing flow through a hollow tube / viscus.
      - › Treatment approaches: anticholinergics, corticosteroids

Nociceptive Pain - Tissue

FIGURE 1 – TYPES OF PAIN



» Pain can be further divided as acute or chronic
  ° Acute
    › Acute onset, then typically resolves within days to weeks
    › Identifiable cause usually exists
    › Difficult to adjust analgesic regimens because intensity can increase and decrease relatively quickly
    › Can usually visualize degree of pain and suffering
  ° Chronic
    › Cause(s) are often less identifiable
    › Duration of several months
    › Often characterized by physical and mental withdrawal (patients often display signs of anorexia, anhedonia, lethargy and sleep changes)
    › More difficult to judge degree of pain and suffering by observation

» Pain can also be characterized based on its timing
  ° Chronic pain – persistent
  ° Incidental pain – pain aggravated by actions such as movement, swallowing, bowel movements or urination
  ° Breakthrough pain – a transitory increase in pain; pain that "breaks through" regular doses of an opioid regimen, including end of dose failure

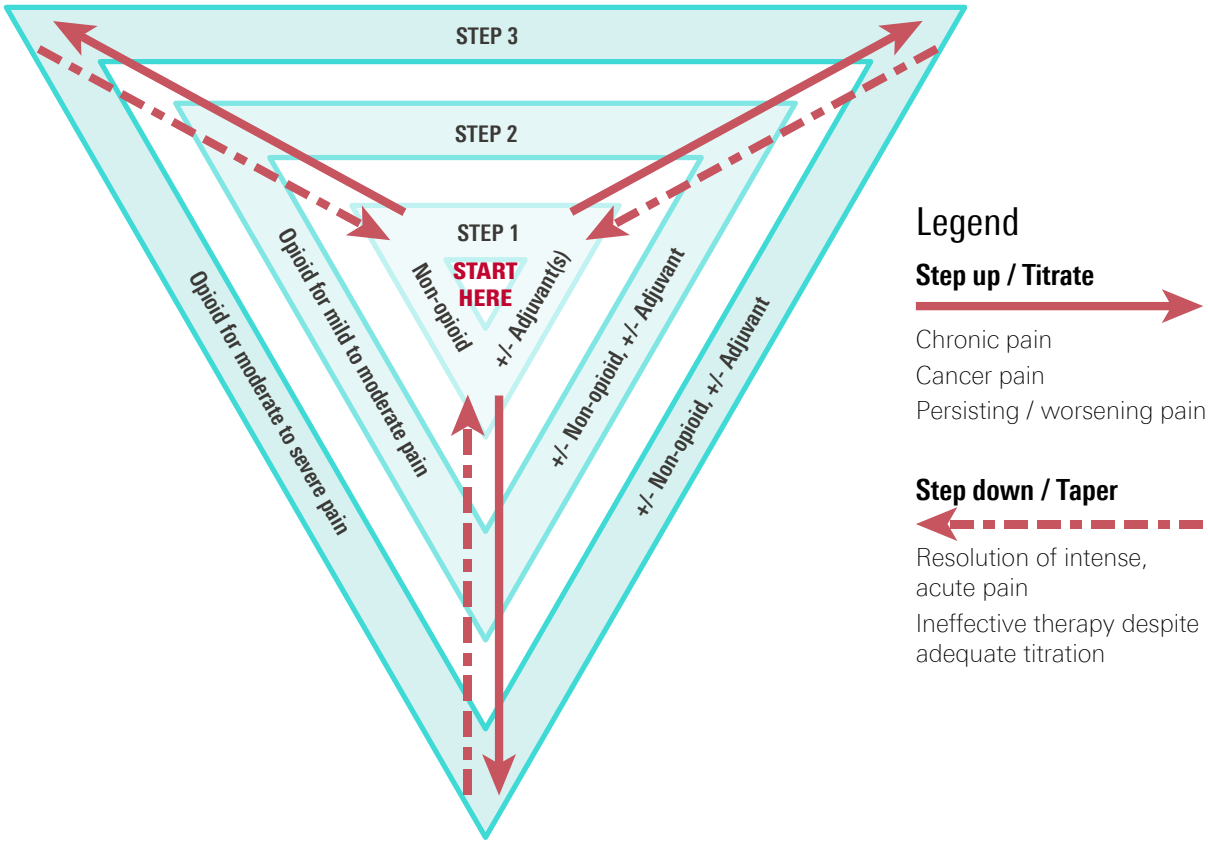
• Pain should be evaluated in a consistent manner. A useful mnemonic is NOPQRSTU.

TABLE 1 – PAIN MNEMONIC

LETTER	PHRASE	EXPLANATION
N	Number of "pains"	Many patients experience pain of more than one type or in more than one location. Each should be identified, categorized and addressed
O	Origin of pain	Knowing the cause of the pain(s) helps guide treatment modalities
P	Potentiating and Palliating factors	Knowing what makes the pain better or worse or what relieves it. Things such as activities, positioning, effect (or lack thereof) from drug therapies
Q	Quality	The words that a patient uses to describe their pain offers insight into the type of pain being experienced
R	Radiation	How and where the pain spreads
S	Severity and suffering	Severity is the intensity of pain assigned by the patient. A variety of pain rating scales exist to allow a patient to report their pain. It is most commonly reduced to a number on a 0-10 scale. Pain ratings should be gathered for pain at its best (lowest score) and worst (highest score) levels. Suffering is the impact that pain has on the patient including the affect it has on other symptoms that the patient may be experiencing.
T	Timing and trend	Timing is the pattern of a patient's pain. Does it come and go? Does it have a pattern? Is it predictable? Trend is the concept that pain may be increasing in frequency or duration and that patients have a tendency to project what will happen to them because of the pain. This can influence overall satisfaction with a given therapy regimen.
U	(Effect on) You (the patient)	How the overall pain experience affects the patient's quality of life (interact with others, ambulate, eat, sleep, etc.)

- Non-pharmacologic approaches to pain control include
  - Massage therapy
  - Chiropractic therapy
  - Therapeutic touch
  - Local application of heat or cold
  - Transepidermal nerve stimulation
  - Accupuncture
  - Biofeedback
  - Cognitive and behavioral therapy
  - Hypnosis
  - Distraction
  - Music therapy
- Pharmacologic therapy is the mainstay of pain management. An expert committee convened by the World Health Organization (WHO) proposed a structured approach to drug selection resulting in the analgesic ladder (**Figure 2**). Originally applied to the management of cancer pain it is widely used for the management of all types of pain. It is based on patient report of the severity of pain.
  - Mild pain: non-opioids (eg, NSAIDs, acetaminophen, aspirin) +/- adjuvant analgesic
  - Moderate pain: weak opioid +/- non-opioid +/- adjuvant analgesic
  - Severe pain: strong opioid +/- non-opioid +/- adjuvant analgesic
- Analgesic drugs are typically prescribed
  - By mouth
  - On a regular schedule – by the clock
  - In a step-wise manner – by the analgesic ladder
  - For the needs of a specific patient – individualized by the type and character of pain experienced by the patient rather than a typical or standard order
  - With attention to detail – ability for patient/caregiver to understand and adhere to the therapeutic plan and includes tenets of rational prescribing (choice of medication, dosage regimen and route of administration)

FIGURE 2 – WHO PAIN LADDER[1]



- Adjuvants should be considered for any magnitude of uncontrolled pain in order to augment analgesia provided by other agents, to treat concurrent symptoms that aggravate pain, and to provide analgesia for specific types of pain
  - » Adjuvant analgesic medication classes include:
    - ° Antiepileptics
    - ° Antidepressants (TCAs, SNRIs)
    - ° Corticosteroids
    - ° Anticholinergics
- Common class effects of NSAIDs include:
  - » Adverse GI effects (eg, ulceration, nausea/vomiting, dyspepsia and diarrhea),
  - » Increased risk of cardiovascular events,
  - » Reduced renal perfusion/renal injury
  - » Impaired platelet function
  - » Potential to worsen pulmonary symptoms
- These class effects occur to varying degrees, depending on choice of NSAID (**Table 2**)
  - » Renal perfusion in elderly patients and platelet function are mostly COX-1 dependent
  - » Because of these effects, NSAIDs are typically avoided in patients with heart disease, renal disease or history of bleeding
    - ° Risks vs. benefits of use should be assessed on an individual basis in the hospice setting
    - ° For treatment of pain in patients with cardiac disease, the American Heart Association recommends, in the following order: acetaminophen, aspirin, tramadol, opioids, non-acetylated salicylates, NSAIDs with low COX-2 selectivity, NSAIDS with moderate COX-2 selectivity and lastly COX-2 selective NSAIDs.

1 Adapted from: World Health Organization (WHO) cancer pain ladder for adults, accessed online Dec. 2015 at: http://www.who.int/cancer/palliative/painladder/en/#

TABLE 2 – NSAID CHARACTERISTICS: COX-2 SELECTIVITY AND RELATIVE GI/CARDIOVASCULAR RISKS

NSAID	COX-2 SELECTIVITY	GI RISK	CARDIOVASCULAR RISK
Salicylates			
Aspirin	Low	Moderate	Low
Diflunisal	Moderate	Moderate	Unknown
Salsalate	Unknown	Low	Unknown
Propionic acid derivatives			
Ibuprofen	Moderate	Low	Moderate – High
Ketoprofen	Low	Moderate	Unknown
Naproxen	Low	Moderate – High	Low
Oxaprozin	Low	High	Unknown
Acetic acid derivatives			
Diclofenac	High	Moderate	High
Etodolac	High	Low	Moderate
Indomethacin	Low	Moderate – High	Moderate
Ketorolac	Low	High	Unknown
Nabumetone	Moderate	Low	Unknown
Sulindac	Moderate	Moderate	Unknown
Enolic acid derivatives			
Meloxicam	High	Low	Moderate
Piroxicam	Moderate	High	Low
Selective COX-2 inhibitor			
Celecoxib	Highest	Low	Moderate – High

- Choosing an opioid
  - » Consider prior use and allergy / intolerance history (see appendix for opioid intolerance algorithm)
  - » In patients with renal impairment
    - ° Transdermal fentanyl, extended release oxycodone and methadone are preferred long-acting opioids
    - ° Hydromorphone, oxycodone and parenteral fentanyl are preferred short-acting opioids
  - » In patients with hepatic impairment
    - ° Codeine and tramadol are unlikely to provide effective analgesia as they are prodrugs that require hepatic conversion to their active forms
  - » Presence of dysphagia / unavailability of the oral route
    - ° Transdermal fentanyl or methadone are preferred long-acting opioids
  - » Consider cost

    - Morphine is the most cost-effective short-acting opioid and should be used preferentially unless clinically inappropriate
    - Extended release oxycodone is substantially more expensive than extended release morphine or transdermal fentanyl
    - Oral / transmucosal / buccal / sublingual fentanyl dosage forms are extremely expensive and may not be affordable in the current hospice reimbursement environment
  - Meperidine is not recommended due to its short duration of action and potential for accumulation of its active metabolite (normeperidine) which may lead to CNS toxicity

- If allergy or intolerance is reported (see appendix for opioid intolerance algorithm)
  - Opioids are structurally different from one another, but can be grouped into three classes
    - Phenanthrenes: codeine, morphine, hydromorphone, oxycodone, hydrocodone, oxymorphone
    - Phenylpiperidines: fentanyl
    - Phenylheptanes: methadone

- When starting opioids
  - Lower initial doses (eg, one-half of doses listed in drug table) can be considered in frail / elderly patients or those more susceptible to fatigue (eg, heart failure)
  - Routine bowel care regimens should be started in all patients taking opioids on a routine basis in order to prevent opioid-induced constipation
  - Nausea/vomiting are common, but usually transient and self-limiting. This type of nausea vomiting is best treated with haloperidol, a potent dopamine blocker at the chemoreceptor trigger zone (CTZ)

- When adding a long-acting opioid
  - When possible, use the same opioid as used for PRN doses to simplify calculations and make it easier to identify causative medication(s) if adverse effects develop
  - Add typical 24-hour PRN use to determine appropriate 24-hour amount of long-acting opioid, then divide appropriately based on long-acting opioid selection (eg, BID for morphine ER)

- Calculating / adjusting PRN / rescue doses
  - A typical PRN dose is 10-15% of daily maintenance dose of opioid amount (this "rule" is not evidence based, rather common practice). As a result the amount of medication necessary to manage PRN pain can vary depending on whether the breakthrough event is spontaneous or purposeful
  - While the duration of effect of oral immediate-release opioids (transmucosal fentanyl excluded) is typically 4 hours (oxymorphone 4-6 hours, methadone 4-8 hours) it may be necessary to prescribe immediate-release opioids on a 1-2 hour schedule in some cases
  - The PRN dose should be adjusted with every titration of the long-acting opioid regimen

- Titrating an opioid regimen
  - Consider dose titration in patients requiring 3-4 breakthrough doses in a 24-hour period
    - increase total daily dose of opioid by 25-50% for mild to moderate pain
    - increase total daily dose of opioid by 50-100% for moderate to severe pain
    - doses of short-acting single-ingredient opioids can be safely increased q 2 hours
    - doses of long-acting oral opioids can be safely increased q 24 hours (except methadone and fentanyl)

- Decreasing/ tapering opioid doses
  - May be required as a result of the addition of an opioid-sparing medication, non-pharmacologic intervention or emergence of side-effects
    - In instances where pain is well controlled but experiencing dose-related intolerable side-effects decrease the basal opioid by about one-third and leave the rescue dose unchanged
    - In instances where pain is not controlled and the patient is experiencing opioid-related intolerable side-effects reduce the opioid dose by one-third to one-half and consider a co-analgesic or rotate opioids
  - Reasons to convert from one opioid to another include:

- Lack of adequate response to increasing dose (when assessment finds that a dose increase is appropriate)
- Development of adverse effects such as nausea, vomiting, constipation, sedation, confusion, hallucinations, delirium, urinary retention, postural hypotension or allergic reaction
- Change in status requiring a different formulation or route of administration such as difficulty swallowing or conditions that alter absorption of transdermal dosage forms

» Differences and limitations exist between opioid equianalgesic tables. Patient-specific factors that influence the success of conversions include

- Renal and hepatic function
- Patient-specific opioid receptor effects (pharmacogenomics)
- Influence of opioid exposure (current and historic)
- Concurrent use of interacting medications
- Comorbidities

» Study-specific factors that influence conversions include

- Single vs. multiple dose studies
- Acute pain vs. chronic pain studies
- Source of study (clinical trial vs. pharmaceutical manufacturer guideline)
  - (Avoid using the fentanyl package insert, which typically is overly conservative when converting to transdermal fentanyl and is not recommended to convert from transdermal fentanyl to other opioids)

» Multiple equianalgesic tables notwithstanding, it is important to recognize that different conversion ratios can exist depending on the direction of the conversion (ie, morphine to hydromorphone vs. hydromorphone to morphine). As such patients should be monitored closely for effect and side-effect with all conversions

» When switching from one opioid to another, consider the need for reduction due to incomplete cross tolerance (typical reduction is to reduce calculated equivalent dose by 25-50%).

» No evidence currently exists to support the idea that cachectic patients should not be prescribed transdermal fentanyl.

- Other general insights
  - » Rectal administration of opioid suppositories or enemas are subject to variable analgesic effectiveness rates depending on placement within the rectal vault. Suppositories inserted low into the vault (just past the rectal sphincter) avoid first-pass metabolism.
  - » Significant inter-patient differences exist in the rectal absorption of medications
  - » While good analgesia has been reported with rectal administration of controlled release morphine and oxycodone this is not an FDA approved route of administration
  - » Concentrated morphine and oxycodone solution are poorly absorbed through the oral mucosa. The pharmacologic effects of these medications via sublingual or buccal administration is primarily due to swallowing the solution.

Nociceptive Pain - Tissue

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)				
Aspirin (Ecotrin, Bayer)	Initial: 2.4 to 3.6 grams/ day in divided doses MDD: 5.4 grams/day	Capsule: 81mg, 325mg, 500mg Capsule (EC)*: 325mg Chewable tablet: 81mg Suppository: 300mg, 600mg Tablet: 81mg, 165mg, 325mg, 650mg Tablet (EC)*: 81mg, 325mg, 500mg	• Monitor for antiplatelet effects • May cause GI upset/ take with food or milk • Inexpensive	Y/N*
Choline magnesium Trisalicylate (Trilisate)	Initial: 1,000mg PO BID MDD: 4,500mg/day	Oral solution: 500mg/5ml (240ml) Tablet: 500mg, 750mg, 1,000mg	• Do not use with salicylates or aspirin allergy • Less GI effects • NSAIDs are drug of choice for bone pain • May cause GI upset/ take with food or milk	Y
Ibuprofen (Advil, Motrin)	Initial: 400-800mg PO Q 6-8h MDD: 3,200mg/day	Capsule: 200mg Chewable tablet: 50mg, 100mg Oral suspension: 100mg/5ml, 40mg/ml Tablet: 200mg, 400mg, 600mg, 800mg	• NSAIDs are drug of choice for bone pain • Can be used for paraneoplastic fever/sweating • Take with food/milk • May cause GI upset/ take with food or milk	-
Naproxen sodium (Aleve, Naprosyn)	Initial: 250-500mg PO BID MDD: 1,500mg/day	Capsule: 220mg Cream: 10% Oral suspension: 125mg/5ml Tablet: 220mg, 250mg, 375mg, 500mg Tablet (ER)*: 375mg, 500mg, 750mg Tablet (DR)*: 375mg, 500mg	• NSAIDs are drug of choice for bone pain • Long acting NSAID • 275mg naproxen sodium = 250mg naproxen • May cause GI upset/ take with food or milk • OTC inexpensive	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER				
Acetaminophen (Tylenol)	Initial: 325-650mg PO Q4-6h or 1,000mg PO 6-8h MDD: 3,000-4,000mg/day	Chewable tablet: 80mg, 160mg Geltab: 500mg, 650mg Oral solution: 160mg/5ml, 500mg/15ml Solution for injection: 10mg/ml Suppository: 80mg, 120mg, 325mg, 650mg Tablet: 325mg, 500mg Tablet (ER)*: 650mg	• Drug of choice for arthritic pain	Y/N*
Ketamine (Ketalar)	Initial (PO): 10-25mg PO TID-QID. May titrate as rapidly as 5mg per dose or 20mg per day. Additional doses can be given as needed at 1/10th to 1/6th of the total daily scheduled amount although as-needed use is not well-studied. Initial (SQ infusion): 100mg over 24 hours Initial (IV infusion): 0.6mg/kg over 4 hours Note: for infusions, consider administering daily for two 5-day infusion periods, separated by a 2-day ketamine-free interval MDD (PO): typically 200mg/day, although daily doses as high as 900mg/day have been reported. MDD (SQ infusion): 500mg/day MDD (IV infusion): 100mg over 4 hours	Injection: 10mg/ml, 50mg/ml, 100mg/ml	• Not first line therapy • Has been studied in nearly every type of pain, but with conflicting results • Consider when: other agents have been tried and failed or were only partially effective and in patients with multimodal pain with a neuropathic component • Disassociative anesthetic used at subanesthetic doses for analgesia • NMDA receptor antagonism thought to provide benefits in reducing opioid tolerance and improved neuropathic pain. Because of mechanistic overlap with methadone (both block NMDA), patients maintained on methadone may be less likely to benefit with ketamine use. • May allow decreased opioid requirements. Consider an empiric opioid dose reduction of 25% if commencing with ketamine for pain. If respiratory depression occurs with concomitant use of ketamine and opioids, reduce opioid dose as ketamine is unlikely to cause significant respiratory depression *(Continued on next page)*	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER (CONTINUED)				
Ketamine (Ketalar) *(Continued)*			• Avoid in patients with schizophrenia (and similar disorders), those with raised intracranial pressure and those with conditions where increased BP/ HR would be hazardous • May cause both psychiatric (eg, euphoria, psychosis, delirium) and somatic (eg, hypertension, tachycardia, hypersalivation, raised intracranial pressure, GI distress, and cystitis) side effects. Daily doses higher than 400mg/day are significantly more likely to cause adverse effects. Approximately half of patients will experience adverse effects when using ketamine at analgesic doses, although they do not always lead to discontinuation. • In some cases, adverse effects can be mitigated with other medications (eg, haloperidol for delirium, labetalol for HTN/tachycardia)	-
Tramadol (Ultram, Conzip, Qdolo)	Initial (IR): 50-100mg Q4-6h PRN Initial (ER) 100mg PO QD MDD (IR): 400mg/day (300mg/day if age > 75) MDD (ER): 300mg/day	Capsule (ER)*: 100mg, 200mg, 300mg Tablet: 50mg, 100mg Tablet (ER)*: 100mg, 200mg, 300m Oral solution: 5mg/ml	• May lower seizure threshold • Potentially beneficial in treatment of neuropathic pain • If CrCl <30ml/min: do not dose IR tablet more often than Q12 hours, ER form contraindicated • Avoid in patients with liver impairment; conversion to active form impaired resulting in inadequate analgesia • May increase risk of hypoglycemia • Oral solution expensive	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OPIOID / ACETAMINOPHEN (APAP) COMBINATION PRODUCTS				
Codeine/APAP (Tylenol #3 & #4)	Initial: 300/15-300/30mg PO TID-QID PRN MDD: 4,000mg APAP/day; 360mg codeine/day	Tablet: 15/300mg, 30/300mg, 60/300mg	• Avoid if renal impairment; even small doses have been reported to cause adverse effects • Avoid in patients with liver impairment; conversion to active form impaired resulting in inadequate analgesia • Not typically preferred; extensive conversion to morphine resulting in increased opioid-effects in patients who are CYPD6 ultrarapid metabolizers • Monitor combined use of all APAP sources so not to exceed daily maximum of 3-4 grams per day from all sources • Causes more GI upset than other opioids • Doses ≥60 associated with considerably higher incidence of side effects and fail to produce proportional improvements in pain	Y
Hydrocodone/APAP (Norco, Vicodin, Lortab)	Initial: 5/325mg tablet 1-2 PO Q4-6 hours PRN MDD: 4,000mg APAP/day	Oral solution: 7.5-325mg/15ml, 10-300mg/15ml, 10-325mg/15ml Tablet: 5/300mg, 5/325mg, 7.5/300mg, 7.5/325mg, 10/300mg, 10/325mg	• Monitor combined use of all APAP sources so not to exceed daily maximum of 3-4 grams per day from all sources • 300mg strengths more expensive than 325mg • Oral solution expensive	Y
Oxycodone/APAP (Percocet, Primlev, Roxicet)	Initial: 5/325mg tablet 1-2 PO Q4-6 hours PRN MDD: 4,000mg APAP/day	Oral solution: 5/325mg in 5ml Tablet: 2.5/325mg, 5/300mg, 5/325mg, 7.5/300mg, 7.5/325mg, 10/300mg, 10/325mg	• Monitor combined use of all APAP sources so not to exceed daily maximum of 3-4 grams per day from all sources • 300mg strengths more expensive than 325mg • More expensive than Oxycodone IR tablets	Y

Nociceptive Pain - Tissue

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OPIOID ANALGESICS				
Codeine	Initial: 15-30mg PO TID-QID MDD: 360mg/day	Oral solution: 30mg/5ml Tablet: 15mg, 30mg, 60mg	• Avoid if renal impairment; even small doses have been reported to cause adverse effects • Avoid in patients with liver impairment; conversion to active form (morphine) impaired resulting in inadequate analgesia • Not first line therapy • Causes more GI upset than other opioids	Y
Fentanyl (Sublimaze, Duragesic)	Initial (IV/SQ): 25-50mcg q1-2h PRN Initial (transdermal): not for opioid naïve patients; starting dose dependent on prior opioid use and tolerance MDD: none	Solution for injection: 0.05mg/ml (50mcg/ml) Transdermal patch: 12mcg/hr, 25mcg/hr,37.5mcg/hr, 50mcg/hr,62.5mcg/hr, 75mcg/hr,87.5mcg/hr, 100mcg/hr	• See fentanyl monograph for additional details • Drug of choice if renal impairment • Change patch every 72 hours unless documented history of end of dose failure • Avoid in patients with unstable pain • Patch not for opioid naïve patients • Useful if patient cannot swallow • Difficult to titrate • Do not cut patches • 12mcg/hr, 37.5mcg/hr, 62.5mcg/hr and 87.5mcg/hr patches are more expensive than other strengths	-
Hydrocodone ER (Zohydro, Hysingla)	Initial (ER, 12-hr): 10mg PO Q12 hours (opioid naïve) Initial (ER, 24-hr): 20mg PO QD (opioid naïve) MDD: none	Capsule (ER, 12-hr): 10mg, 15mg, 20mg, 30mg, 40mg, 50mg Tablet (ER, 24-hr): 20mg, 30mg, 40mg, 60mg, 80mg, 100mg, 120mg	• For chronic pain only • Abuse deterrent preparations • Expensive	N
Hydromorphone (Dilaudid, Exalgo)	Initial (PO, IR): 1-2mg q3-4h PRN Initial (PO, ER): not for opioid naïve patients; starting dose dependent on prior opioid use and tolerance Initial (PR): 3mg q4-8h PRN Initial (SQ/IV): 0.2-0.6mg q2-3h PRN MDD: none	Oral solution: 1mg/ml Solution for injection: 0.2mg/ml, 1mg/ml, 2mg/ml, 4mg/ml, 10mg/ml Suppository: 3mg Tablet: 2mg, 4mg, 8mg Tablet (ER)*: 8mg, 12mg, 16mg, 32mg	• Drug of choice if renal impairment • ER Tablets and suppositories are expensive	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OPIOID ANALGESICS (CONTINUED)				
Methadone (Dolophine)	Individualized dosing	Oral solution: 5mg/5ml, 10mg/5ml,10mg/ml Solution for injection: 10mg/ml Tablet: 5mg, 10mg, 40mg	• See methadone monograph for additional details • Use with extreme caution • Useful for both nociceptive and neuropathic pain • Drug of choice if renal impairment • Long, variable half-life (average=20-35 hours, may be up to 130 hours in some patients) • May increase risk of hypoglycemia; when initiating at doses ≥ 40mg/day, consider blood glucose monitoring • Call clinical pharmacist for dosage recommendations • Inexpensive	Y
Morphine (Roxanol, MSContin)	Initial (PO, IR): 5-15mg PO Q1-4 hours PRN Initial (PO, ER): Starting dose based on immediate release equivalent dose Initial (SQ/IV): 2-5mg Q2-4 hours MDD: none	Capsule (ER)*: 10mg, 20mg, 30mg, 40mg, 45mg, 50mg, 60mg, 75mg, 80mg, 90mg, 100mg, 120mg Oral solution: 10mg/5ml, 20mg/5ml, 20mg/ml Solution for injection: 0.5mg/ml, 1mg/ml, 2mg/ml, 4mg/ml, 5mg/ml, 8mg/ml, 10mg/ml, 15mg/ml, 25mg/ml Suppository: 5mg, 10mg, 20mg, 30mg Tablet: 15mg, 30mg Tablet (ER)*: 15mg, 30mg, 60mg, 100mg, 200mg	• Opioid of choice in the hospice setting • Repeated dosing in patients with renal impairment can result in adverse effects due to metabolite accumulation / opioid-induced neurotoxicity • Able to be administered rectally • ER capsules and suppositories are expensive	Y/N*
Oxycodone (Roxicodone, Oxycontin)	Initial (IR): 5-10mg PO/ PR/SL q4-6h Initial (ER): 10mg PO/ PR q12h for opioid naïve patients MDD: none	Capsule: 5mg Oral solution: 5mg/5ml, 20mg/ml Tablet: 5mg, 15mg, 30mg Tablet (ER)*: 10mg, 15mg, 20mg, 40mg, 60mg, 80mg	• Drug of choice if renal impairment • ER tablets and 20mg/ml oral solution are expensive	Y/N*
Oxymorphone (Opana)	Initial (IR): 10-20mg PO q4-6h PRN Initial (ER): 5mg PO q12h Initial (Inj): 0.5mg IV/IM q4-6h PRN	Solution for injection: 1mg/ml Tablet: 5mg, 10mg Tablet (ER)*: 5mg, 7.5mg, 10mg, 15mg, 20mg, 30mg, 40mg	• Administer on an empty stomach • Expensive	Y/N*

References

- Aleksandrova, L. Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism, J Psych Neurosci, 2017.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 320, 333-48, 359-60, 367-79, 415-30, 467-74, 505-9.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 159-169.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 2: Cancer pain management, accessed online Nov. 2015 at: http://www.ipcrc.net/epco/EPEC-O%20M02%20Pain/EPEC-O%20M02%20Pain%20PH.pdf
- Faskowitz, A. et al. Methadone-Induced Hypoglycemia, Cellular and Molecular Biology, 2013, 33:537-42.
- Fine, P. The Hospice Companion, 2nd ed, Oxford University Press, 2012.
- Flory, J. et al. Methadone Use and the Risk of Hypoglycemia for Inpatients with Cancer Pain, Journal of Pain and Symptom Management, 2015, article in press.
- Fournier, J. et al. Tramadol Use and the Risk of Hospitalization for Hypoglycemia in Patients with Noncancer Pain, JAMA Internal Medicine, 2015, Vol. 175, No. 2, pp. 186-93.
- Gould, et al. Ketamine mechanism of action: Separating the wheat from the chaff, Neuropsychopharmacology Reviews, (2017)42:368-9.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 587-626,654-9,661-92,698-704,706-727, 1555.
- Ketamine, Lexicomp: Mechanism of action.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Marchetti, F. et al. Efficacy and safety of oral ketamine for the relief of intractable chronic pain: A retrospective 5-year study of 51 patients, Eur J Pain; 2014.
- McPherson ML. Demystifying Opioid Conversion Calculations: A Guide to Effective Dosing-American Society of Health System Pharmacists; 2010
- Quibell, R. et al. Therapeutic Reviews: Ketamine, Journal of Pain and Symptom Mgmt, 2015;50(2):268-78.
- Quill TE, Bowe KA, et al. Primer of Palliative Care 6th edition, American Academy of Hospice and Palliative Medicine; 2014
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 43-74,337.
- Rigo, FK, et al. Management of neuropathic chronic pain with methadone combined with ketamine: A randomized, double blind, active-controlled clinical trial, Pain Physician, 2017;20:207-15.
- Rosenquist, E. et al. Overview of the treatment of chronic pain, UpToDate, literature review current through Nov. 2015.
- Twycross R, Wilcock A, Howard P editors. Palliative Care Formulary 5. Palliativedrugs.com Ltd 2014
- World Health Organization. Cancer Pain Relief 2nd edition. http://www.whqlib.who.int/publications/9241544821.pdf

Refractory Symptoms Requiring Continuous Palliative Sedation

DEFINITION

Continuous palliative sedation is the use of sedative medications to reduce consciousness until death in terminally ill patients whose symptoms are so severe and refractory that they would suffer if not sedated.

Disambiguation: This monograph describes continuous palliative sedation, not temporary / respite sedation.

APPROPRIATE USE IN HOSPICE PATIENTS[1]

- Continuous palliative sedation may be considered when symptoms are severe and refractory to standard drug therapies, including:
  - Agitated delirium
  - Pain
  - Dyspnea
  - Nausea / vomiting
  - Existential distress
- Patients should be sedated only to a level that is proportionate to their present and/or expected symptom burden.
- Continuous palliative sedation will be maintained until death, so patients should be DNR (do not resuscitate) and have a prognosis of less than 2 weeks.

DRUG SELECTION[1]

- The intravenous route is preferred for palliative sedation, although subcutaneous and rectal administration can often provide adequate sedation.
- Many hospice programs preferentially utilize the subcutaneous (SQ) route over the intravenous (IV) route due to ease, familiarity, and cost.
  - Appropriate for SQ administration: midazolam, lorazepam, phenobarbital
  - Inappropriate for SQ administration: diazepam, propofol
- Although drug selection algorithms have been proposed, prescriber experience and knowledge of sedative medications, patient characteristics (e.g., prognosis, allergies, intolerances, previous failure), and facility protocols influence sedative choice.
- Benzodiazepines are 1st line therapy.
  - Midazolam is by far the most common benzodiazepine used for palliative sedation because its short time to peak and short half-life are ideal for this purpose, but lorazepam and diazepam can provide equal levels of sedation.
  - Paradoxical agitation can typically be overcome by increasing doses.[2]
  - Fluid volume necessitated with IV infusions varies across agents and may affect drug selection.
    - Fluid excess can result in third spacing or pulmonary edema
    - Fluid volume needed with infusion is midazolam < lorazepam << diazepam
- Despite its pharmacological shortcomings (see Drug Information table), phenobarbital is generally employed as 2nd line therapy in the hospice setting.
- Compounded phenobarbital suppositories have been reported to provide adequate sedation, including in the home setting, allowing fulfillment of patients' wishes to die at home and avoiding hospital or hospice inpatient unit admissions.[3]
- Propofol is a very effective sedative, but is uncommonly used in the hospice setting for palliative sedation due to complexities with dosing, monitoring, and safely running the infusion.

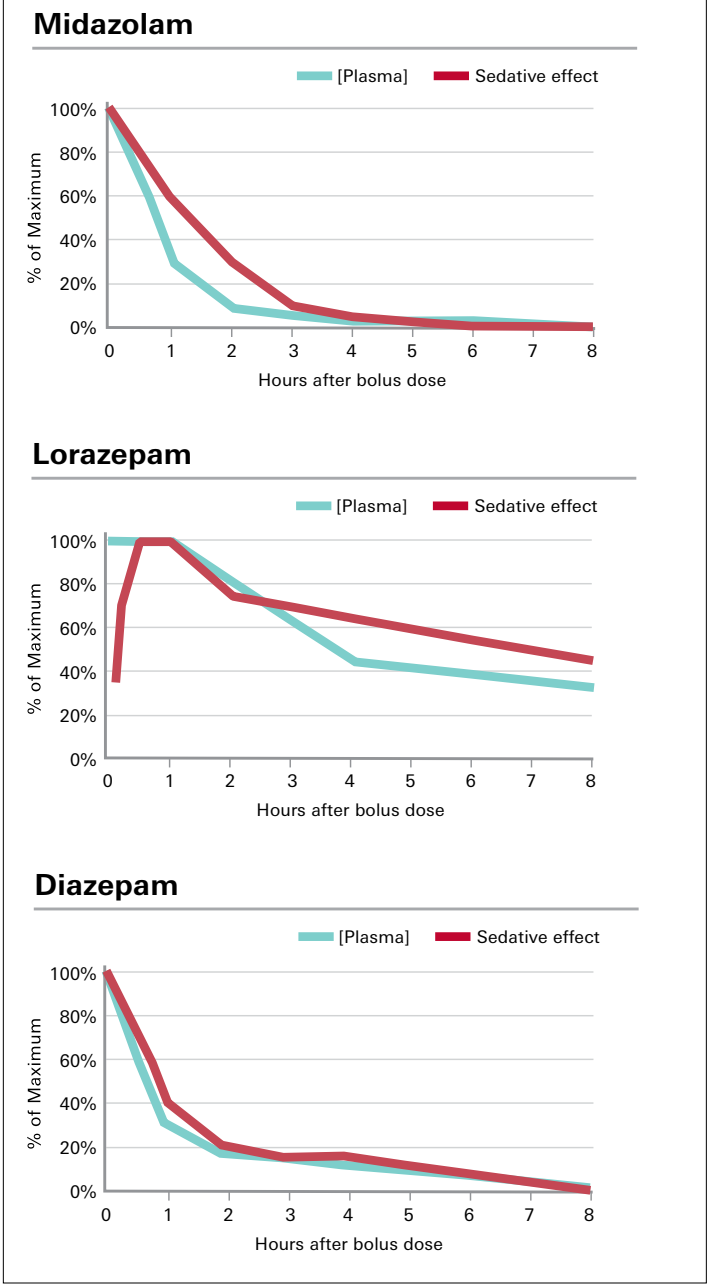
PHARMACOKINETIC & PHARMACODYNAMIC CONSIDERATIONS[1]

- Equisedative dosing conversion strategies between benzodiazepines may be sought by clinicians looking to achieve effective sedation. However, these values are inexact and their comparative sedative effect differs between boluses and infusion, and even continues to change over time during infusions.
  - For example, one hour after starting infusions, 2mg midazolam is approximately equal to 1mg of lorazepam; then, the amount of midazolam required to equal 1mg of lorazepam grows, stabilizing at 4-5mg midazolam for each 1mg of lorazepam at 6 hours and beyond.
- The sedative effects of midazolam and diazepam are relatively immediate (within a few minutes following

IV boluses) and generally mirror their respective therapeutic concentrations, whereas the peak sedative effect of lorazepam occurs about 30 minutes following an IV bolus dose (**Figure 1**).

- Despite its relatively slow rise to maximal sedative effect when compared to midazolam/diazepam, lorazepam maintains 65% of its maximal effect 4 hours after a bolus dose versus 16% for diazepam and 5% for midazolam (**Figure 1**).

FIGURE 1 – BENZODIAZEPINE COMPARISON OF PLASMA CONCENTRATION VS. SEDATIVE EFFECT FOLLOWING IV BOLUS[1]



ROLES OF OPIOIDS AND ANTIPSYCHOTICS[1]

- Opioids should not be used for the purpose of sedation, but should be continued at previous doses in patients already receiving them for pain or other symptom management at the time sedation is started.
- Once a patient is effectively sedated, it is reasonable to discontinue as needed opioid orders and instead provide as needed sedative boluses and/or titrate the sedative.
- Haloperidol is an effective antiemetic and the drug of choice for agitated delirium in the hospice setting, but even at doses of 20mg/hour or higher, it does not reliably produce effective sedation. Therefore, it should generally not be used for continuous palliative sedation, unless the indication for sedation is delirium, nausea/vomiting, or another haloperidol-responsive symptom.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BENZODIAZEPINES				
Midazolam[1,4] (Versed)	Initial (IV bolus): 2-5mg IV Q5 min until sedated. May consider 10mg boluses if distressing life-ending event. Initial (SQ bolus): 2-5mg SQ Q15 min until sedated. May consider 10mg boluses if distressing life-ending event. Initial (IV/SQ infusion): 1-2mg/hour following a bolus dose OR Approximately 50% of the bolus dose required for sedation hourly (i.e., required 10mg bolus, then 5mg/hour) MDD (IV/SQ boluses): Doses beyond 20mg offer minimal incremental benefit. SQ boluses should not exceed 2ml per site. MDD (IV/SQ infusion): Doses as high as 50mg/hour have been used, but limited utility beyond 20mg/hour (see comments). SQ infusions should not exceed 3ml/hour per site.	Solution for injection: 1mg/ml, 5mg/ml	• Most common medication used for palliative sedation • Effective in more than 80% of cases • IV infusions can be titrated as frequently as every 1 hour • Typical infusions are 1-5mg/hour • Once 20mg/hour reached, consider adding an additional sedative or rotating to a different sedative • Dilution » Diluted with NS or D5W to 0.5-1mg/ml for IV infusions » Can be administered undiluted for SQ infusions up to maximum 3ml per hour per site • Higher doses often needed in patients with history of IV drug abuse or benzodiazepine tolerance	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BENZODIAZEPINES				
Lorazepam[1,4] (Ativan)	Initial (IV/SQ boluses): 4mg IV Q4 hours Initial (IV/SQ infusion): 1mg/hour following a bolus dose MDD (IV/SQ infusion): Typically 10mg/ hour although doses as high as 30mg/ hour have been used (see comments). SQ infusions should not exceed 3ml/hour per site.	Solution for injection: 2mg/ml, 4mg/ml	• Compared with midazolam: » Less commonly used » Less interindividual variability with sedative effect » Longer duration of action, so beneficial if boluses preferred over infusion » Slower time to peak sedative effect (up to 30 minutes with IV administration, see Figure 1) » Infusions cannot be prepared on site at hospice inpatient units (unless pharmacy on-site) • Propylene glycol diluent » Solution for injection contains significant amount of propylene glycol (PG), which can accumulate to toxic levels » Symptoms of PG toxicity include refractory hypotension, arrhythmia, hemolysis, multiorgan failure » Potential for PG toxicity typically limits maximum dosing to 10mg/ hour, although doses as high 30mg/ hour have been used • Solutions for IV infusion are typically prepared as 20mg or 40mg in 250ml D5W • Higher doses often needed in patients with history of IV drug abuse or benzodiazepine tolerance	-
Diazepam[1,4] (Valium)	Initial (IV bolus): 5-10mg Q5 minutes MDD (IV bolus): 30mg per bolus	Solution for injection: 5mg/ml	• Uncommonly used for palliative sedation • Do not administer subcutaneously • IV infusion is not recommended due to precipitation and adsorption of drug to infusion bags and tubing. Therefore, should not be used for long-term sedation. • If midazolam use is prohibited or unavailable, IV diazepam is preferred over lorazepam in managing severe, emergent symptoms (e.g., exsanguination) because of much shorter time to onset (1 minute) and peak (2-5 minutes) • Administer IV boluses of undiluted solution for injection by slow IV push not to exceed 5mg/minute • Higher doses often needed in patients with history of IV drug abuse or benzodiazepine tolerance	-

Refractory Symptoms Requiring Continuous Palliative Sedation

OnePoint® PATIENT CARE

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NON-BENZODIAZEPINES				
Phenobarbital[1,3-4] (Luminal)	Initial (IV/SQ bolus): 200mg Q 30 minutes until sedated then 10% of sum of required doses Q12 hours OR 260-1,250mg Q8-12 hours Initial (compounded rectal suppository): three 200mg suppositories rectally initially, repeat once in 3-4 hours, then 400mg every 4-6 hours. MDD (IV/SQ bolus): 1,250mg per dose (3,750mg/day) (SQ boluses may require several sites to limit volume per bolus per site) MDD (compounded rectal suppository): not established for this indication; consider double MDD of solution for injection considering 50% rectal bioavailability.	Solution for injection: 65mg/ml, 130mg/ml Suppository: compounded products only (availability may vary)	• Considered a more potent sedative than midazolam • Often used 2nd line if midazolam fails • High initial doses can be considered if using 2nd line following inadequate sedation with optimally titrated midazolam • Lacks ideal properties for palliative sedation: » Slow onset of sedative effect (up to 30 minutes following injections) » Long half-life (up to 5 days) makes titration difficult » Accumulates with repeated dosing • Solution for injection is expensive; may round doses to nearest vial size to reduce costs • IV boluses should be diluted in 10ml of NS or D5W and administered slowly, not exceeding 100mg/min • Continuous infusions are not necessary due to the long half-life • Suppositories: » Inexpensive » 50% bioavailability » Rectal absorption / time to onset is relatively slow (up to 12 hours), so consider loading/bridging with other sedatives	-
Propofol[1-4] (Diprivan)	Initial (IV): 0.5-1mg/kg bolus by slow IV push, followed by continuous infusion of 1mg/kg/hour with boluses of 10-100mg as needed. MDD (IV): unlikely to apply published maximum doses in this setting due to lack of viable alternatives.	Emulsion for injection: 10mg/ml	• Rarely used in the hospice setting due to complexities with dosing, monitoring, and safely running the infusion. • Infusions can be titrated by up to 10mcg/kg/min every 20 minutes • Additional sedative agents like benzodiazepines and barbiturates do not generally offer any meaningful additive sedative effect and therefore, titration of propofol is preferred versus combining with other sedatives.	-

References

1. Bodnar, J. et al. A review of agents for palliative sedation/continuous deep sedation: pharmacology and practical applications, Journal of Pain & Palliative Care Pharmacotherapy, 2017; 31(1): 16-37.
2. Irwin, S. et al. Clarifying Delirium Management: Practical, Evidence-based, Expert Recommendations for Clinical Practice, Journal of Palliative Medicine, 2013; 16(4): 423-34.
3. Setla, J. et al. Home palliative sedation using phenobarbital suppositories: Time to death, patient characteristics, and administration protocol, American Journal of Hospice & Palliative Medicine, 2019; 36(10): 871-6.
4. Lexicomp drug monographs, Wolters-Kluwer Health, 2020.

DEFINITION

Sialorrhea is the inability to handle oral secretions that can lead to drooling or a gurgling sound in the back of the throat. This can be a result of increased saliva production or a decreased ability to handle normal production as is seen commonly during the final days of life and with some terminal neurological conditions such as ALS.

Thick pulmonary secretions can be the result of infection, disease process (such as COPD) or inadequate muscle tone / forceful enough cough to expectorate (as in ALS).

CAUSES

- Sialorrhea
  - » Medications – antipsychotics (particularly clozapine and risperidone), ketamine, cholinergic agents such as pilocarpine
  - » Commonly observed in patients with neurological conditions such as ALS, Parkinson disease, myasthenia gravis
  - » Also seen in patients with acquired brain injury, cerebral palsy, cerebrovascular disease, intellectual disability, multiple sclerosis and oromandibular carcinoma
  - » Impaired swallowing
  - » GERD
  - » Cirrhosis
  - » Serotonin syndrome
  - » Oral infections
- Thick pulmonary secretions
  - » Commonly observed in patients with neurological conditions such as ALS, Parkinson disease, myasthenia gravis
  - » Infection
  - » Disease progression
  - » Decreased clearance
  - » Fluid overload

HOW TO RECOGNIZE SYMPTOM

- Sialorrhea
  - » Drooling
  - » Gurgling sound in the back of the throat – "death rattle"
- Thick pulmonary secretions
  - » Lung sounds / crackles
  - » Thick mucus that is difficult to expectorate

CLINICAL INSIGHTS

- Consider positioning the patient to allow gravity to aid in secretion clearing
- Anticholinergic drugs counteract the prokinetic action of metoclopramide
- Anticholinergic drugs and can exacerbate acid reflux symptoms
- Administration of anticholinergics to patients with fever or at times of the year when hot weather is present can lead to heatstroke
- Simultaneous use of two or more anticholinergic drugs or drugs with anticholinergic properties (**Table 1**) increases the risk of side-effects and of CNS toxicity (restlessness, agitation, delirium) particularly with drugs that cross the blood-brain barrier (exception – glycopyrrolate)

TABLE 1 – DRUGS WITH ANTICHOLINERGIC PROPERTIES

Antidepressants	Antihistamines	Antipsychotics	Antispasmodics
Amitriptyline	Diphenhydramine	Olanzapine	Oxybutynin
Doxepin	Promethazine	Chlorpromazine	Tolterodine
Nortriptyline	Meclizine	Quetiapine	Fesoterodine
Paroxetine	Hydroxyzine	Clozapine	Solifenacin
	Loratadine		Flavoxate

- Anticholinergic drugs can affect multiple body systems (**Table 2**)

TABLE 2 – ADVERSE EFFECTS OF ANTICHOLINERGIC DRUGS BY BODY SYSTEM

Visual	Cardiovascular	Gastrointestinal	Urinary Tract	Skin
Blurred Vision	Arrhythmia	Constipation	Hesitancy	Flushing
Dilated Pupil	Tachycardia	Dry Mouth	Urinary Retention	Reduced Sweating
Dry Eyes		Heartburn		

- Sialorrhea
  - » For faster IM absorption, administer atropine, scopolamine and glycopyrrolate in the deltoid muscle rather than the gluteal muscle
  - » Starting therapy early can help prevent secretions, but treatments do not remove existing secretions.
  - » If the patient alternates between sialorrhea and uncomfortable dry mouth, anticholinergics with shorter durations of action, such as atropine or glycopyrrolate may be preferred.
  - » For refractory symptoms, botulinum toxin 7.5-20 units (up to 75 units) may be injected into each parotid gland. Although expensive (~$700/100 units), the effects may last up to 4 months.
- Thick pulmonary secretions
  - » Increased fluid intake will help thin secretions
  - » Anticholinergic medications used to treat sialorrhea can thicken pulmonary secretions, making them more difficult to clear. Some patients may have both sialorrhea and thick pulmonary secretions, so careful balance of therapies is important.
  - » It may be appropriate to treat respiratory infection with antibiotics if symptom reduction is the primary therapeutic goal.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MEDICATIONS USED FOR TREATMENT OF SIALORRHEA				
Amitriptyline (Elavil)	Initial: 25-50mg PO at bedtime (10-25mg if elderly) MDD: 300mg/day	Tablet: 10mg, 25mg, 50mg, 75mg, 100mg, 125mg, 150mg	• Most anticholinergic TCA; may be used to therapeutic advantage to dry secretions • Consider if comorbid depression, insomnia, neuropathic pain • Use with caution in elderly patients due to high risk of adverse effects, including delirium	Y
Atropine	Initial: 1-4 gtts SL q2-4h PRN MDD: not established for this indication	Ophthalmic solution: 1%	• Assess caregiver ability to dose properly • Short duration of action; may be beneficial over other anticholinergics if patient alternates between sialorrhea and uncomfortable dry mouth	Y
Glycopyrrolate (Robinul)	Initial (PO/SL): 0.25-0.5mg PO/SL Q8 hours PRN Initial (Inj): 0.2-0.4mg SQ/IV q4-12h MDD (oral): 8mg/day MDD (Inj): not established for this indication	Solution for injection: 0.2mg/ml Tablet: 1mg, 2mg	• Does not cross blood-brain barrier; therefore, causes less side effects than atropine, hyoscyamine, scopolamine • Poorly and erratically absorbed when given orally • Short duration of action; may be beneficial over other anticholinergics if patient alternates between sialorrhea and uncomfortable dry mouth • Parenteral formulation is expensive	Y
Hyoscyamine (Levsin, Symax, Hyomax, Anaspaz, Nulev)	Initial: 0.125-0.25mg PO/SL q4-6h PRN MDD: 1.5mg/day	Elixir: 0.125mg/5ml Oral disintegrating tablet (ODT): 0.125mg Oral solution: 0.125mg/ml Tablet: 0.15mg, 0.125mg, 0.375mg	• Antacid may interfere with absorption • Also used for G.I./ bladder spasm / cramping	Y
Ipratropium (Atrovent nasal)	Initial: 1-2 sprays (21-42mcg) sublingually QID PRN MDD: 168mcg/day	Nasal spray: 0.03% (21mcg/spray)	• Off label use based on subjective improvements of sialorrhea in a small trial of Parkinson patients. • Does not cross blood-brain barrier; therefore, causes less side effects than atropine, hyoscyamine, scopolamine	-
Scopolamine (Transderm-scop)	Initial: 1 patch q3 days MDD: 3 patches	Patch: 1.5mg/72 hours	• Slow onset of action (up to 8 hours) and time to peak (24 hours) • Also used for vestibular N/V • Occasionally the typical maximum daily dose is exceeded in the hospice setting • More expensive than other agents	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MEDICATIONS USED FOR TREATMENT OF THICK PULMONARY SECRETIONS				
Acetylcysteine (Mucomyst)	Initial (nebulized): 3-5ml of 20% or 6-10ml of 10% nebulized TID-QID PRN Initial (oral): 200mg BID-TID, 300mg BID or 600mg QD PRN MDD (nebulized): 120ml of 20% or 240ml of 10% per day MDD (oral): 1,200mg/day	Solution for injection: 10% (100mg/ml), 20% (200mg/ml)	• Not first line therapy • Oral route is off-label • When giving via nebulizer, give with or after a bronchodilator to optimize effect • When giving via oral route, may reduce frequency to 3x per week for maintenance • Complex administration requires drawing up dose in syringe and may not be practical for some patients • Expensive	-
Guaifenesin (Robitussin, Mucinex)	Initial (IR): 200-400mg PO q4h PRN Initial (ER): 600-1,200mg PO q12h PRN MDD (all forms): 2,400mg/day	Syrup: 50mg/ml, 100mg/5ml, 100mg/6.25ml Tablet: 200mg, 400mg Tablet (ER)*: 600mg, 1200mg	• Tablet is most concentrated dosage form • Encourage fluid intake • Do not crush ER tablets	Y/N*
Metoprolol Tartrate (Lopressor)	Initial: 25mg PO BID MDD: 450mg/day	Tablet: 25mg, 50mg, 100mg	• Off label use based on single, small, non-controlled trial of ALS patients • Not first line therapy • Monitor BP, HR	Y
Potassium Iodide (SSKI)	Initial: 0.3-0.6 ml (300-600mg) PO/SL TID-QID PRN MDD: 2,400mg/day	Oral solution: 1gm/ml	• Dilute each dose of SSKI in one glassful of water, fruit juice, or milk • May crystallize when exposed to cold; warm and shake to dissolve crystals • Discard if the solution turns brownish-yellow in color	-
Propranolol (Inderal)	Initial: 10mg PO BID MDD: 640mg/day	Tablet: 10mg, 20mg, 40mg, 60mg, 80mg	• Off label use based on single, small, non-controlled trial of ALS patients • Not first line therapy • Monitor BP, HR • Avoid if lung disease	Y
Saline Nebs	Initial: 3ml inhalation q4h PRN MDD: 150 mEq	Saline bullets: 0.9%	• Systemic absorption may lead to water retention	-

References

- Andersen, P. et al. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force, European Journal of Neurology, 2012, 19: 360-375.
- Blackhall, L. et al. Amyotrophic lateral sclerosis and palliative care: where we are, and the road ahead, Muscle and Nerve, 45:311-318, March 2012.
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 914-5.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 222.
- Clary, P. et al. Pharmacologic pearls for end-of-life care, Am Fam Phys, 2009; 79(12): 1059.
- Galvez-Jimenez, N. et al. Symptom-based management of amyotrophic lateral sclerosis, UpToDate.com, accessed online Jan. 2015.
- Goldsmith, T. et al. Swallowing disorders and aspiration in palliative care: Assessment and strategies for management, UpToDate, literature review current through Nov. 2015.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 999-1000, 1133-4, 1556-7.
- Hospice and Palliative Care formulary, 5th edition.
- Jenkins, T. et al. The evidence for symptomatic treatments in amyotrophic lateral sclerosis, Current Opinions in Neurology, 2014, 27:524-531.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Lexicomp Online®, Facts and Comparisons Off-Label, Ipratropium Bromide (Sublingual): Sialorrhea (Drooling) in Adults, accessed Nov. 2015.
- Miller, R.G., et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis – drug, nutritional, and respiratory therapies, Neurology, Vol. 73, Oct. 2009, pp. 1218-1226.
- Newall, A, et al. The control of oral secretions in bulbar ALS/MND, Journal of the Neurological Sciences, 139 (Suppl.)(1996)43-44.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 186-187,192-194.
- Simmons, Z. Management Strategies for Patients With Amyotrophic Lateral Sclerosis From Diagnosis Through Death, The Neurologist, Vol. 11, No. 5, 2005.
- Tarcy, D. et al. Management of comorbid problems associated with Parkinson disease, UpToDate, literature review current through Nov. 2015.
- Montagnini, M, et al. Non-Pain symptom management in palliative care, Clinics in Family Practice, Vol. 6(2) June 2004.
- Montagnini, M. et al. Non-pain symptom management in palliative care, Clinics in Family Practice, 2004; 6(2): 395.
- Clary, P. et al. Pharmacologic Pearls for End-of-Life Care, American Academy of Family Physicians 2008, American Family Physician, Vol. 79(12) June 2009.

Seizures (Prevention & Control)

DEFINITION

The clinical manifestation of an abnormal, excessive, hyper-synchronous discharge of a population of cortical neurons; may last seconds to minutes.

CAUSES

- Brain tumors/metastases
- CNS Infection
- Fever
- Head injury/trauma
- Hypoglycemia
- Hypoxia
- Metabolic disturbances
- Stroke/TIA
- Alzheimer's dementia
- Multiple sclerosis
- Renal failure
- Liver cirrhosis
- Drug withdrawal/abrupt discontinuation (eg, anticonvulsants, benzodiazepines, opioids, sedatives, alcohol)
- Opioid toxicity (very high doses)
- Electrolyte imbalances
- Medications (eg, tramadol, bupropion, meperidine, antipsychotics, fluoroquinolone and cephalosporin antibiotics, other antidepressants, severe phenytoin toxicity)
- Sleep deprivation
- Encephalopathy

HOW TO RECOGNIZE SYMPTOM

- Impaired consciousness
- Confusion, loss of attention/awareness
- Muscle stiffness
- Rhythmic jerking of extremities
- Bowel/bladder incontinence
- Respiratory compromise
- Tingling, numbness
- Visual/auditory/olfactory symptoms
- Partial seizures: begin in one hemisphere of the brain
  - » Involuntary contraction or paralysis of muscles may be asymmetric
    - ° Simple partial: no impairment of consciousness
    - ° Complex partial: impairment of consciousness
    - ° Secondarily generalized: partial onset evolving to generalized seizures
- Generalized seizures: clinical manifestations indicate involvement of both hemispheres (bilateral motor symptoms)
  - » Tonic: sudden onset of sustained increase in muscle tone
    - ° Clonic: convulsive movements of rapidly alternating muscular contraction and relaxation
    - ° Tonic-clonic: tonic contractions followed by clonic jerks
    - ° Absence seizures: sudden onset with activity interruption and blank stare
    - ° Myoclonic seizures: brief, sudden, involuntary muscle contractions
    - ° Atonic: sudden loss of muscle tone

CLINICAL INSIGHTS

- Evaluate patient for potentially reversible / treatable causes of seizure
  - » For example, antipsychotics and TCA/SSRI type antidepressants can lower the seizure threshold; evaluate continued therapeutic need / consider reduced doses if possible.
- Before initiating drug therapy to prevent seizure, it is important to differentiate seizures from other forms of involuntary movement, such as drug-induced hyperkinesia, myoclonus or movement patterns related to increased intracranial pressure.
- Prophylactic anticonvulsant therapy in patients with no seizure history with brain tumors or metastases is not recommended (a possible exception is brain metastases from melanoma, where incidence of seizure exceeds 50%)
- For patients with brain tumors and prior seizure, instead of adding or increasing anticonvulsants, first optimize / titrate dexamethasone dosing to control cerebral edema if possible
- Enzyme-inducing antiepileptic drugs, including phenytoin and phenobarbital, can induce metabolism of dexamethasone, reducing its efficacy. Avoid

concurrent use or plan to increase dexamethasone to compensate if concomitant use is unavoidable.

- Anti-seizure medications should be selected based on seizure type (**Figure 1**), potential for adverse effects or drug interactions, feasibility of recommended monitoring parameters and cost.
- Monotherapy is preferred whenever possible; attempt to optimize dose of single medication prior to adding second medication.
- Anticonvulsants as a class commonly cause dizziness, drowsiness, agitation or cognitive impairment as adverse effects
- Most anticonvulsants have significant drug interactions and may require renal/hepatic dose adjustments
- Although clonazepam is the only commonly used benzodiazepine indicated for seizure prevention, others, such as lorazepam and diazepam, have been successfully used on an around-the-clock basis to prevent seizures.
- Patient response, rather than drug serum levels, should be used to guide dosing at end of life in most circumstances, unless overdosing or underdosing is suspected as evidenced by poor seizure control or signs of toxicity.
- Exercise caution when switching between formulations since bioavailabilities can differ (eg, phenytoin capsules/ oral suspension, divalproex DR/ER).
- In patients with dysphagia preventing the use of oral anticonvulsants, the rectal use of oral dosage forms can be considered in some circumstances (see drug table for drug-specific guidance)
- If discontinuing antiepileptic medications, tapering is recommended to prevent rebound seizure.
- Some antiepileptics have a long half-life and may continue to be effective 2-3 days after the last oral dose:
  - » Clonazepam, diazepam, lamotrigine, phenobarbital, phenytoin, topiramate and zonisamide
- In patients with dysphagia preventing the use of oral anticonvulsants, the rectal use of oral dosage forms can be considered in some circumstances (see **Table 1** and **Drug Information** table for drug-specific guidance).

TABLE 1 – RECTAL ADMINISTRATION OF ANTICONVULSANT DRUGS[A]

MEDICATION	CAN IT BE GIVEN RECTALLY?	NOTES
carbamazepine[13,25]	Yes	• Effective and well-tolerated
gabapentin[19]	No	• Not absorbed rectally
lamotrigine[1,2]	Maybe	• Absorbed rectally, but to a lesser degree vs. orally • Dose increases may be necessary
levetiracetam[9,14]	Maybe	• Absorbed rectally with ~50% reduced absorption • Consider 1:2 (oral:rectal) dosing • May cause rectal bleeding
oxcarbazepine[7]	No	• Low rectal bioavailability; unlikely to reach therapeutic levels
phenobarbital[20]	Yes (for prophylactic / maintenance treatment only)	• Total rectal absorption is comparable to the oral route when oral solution or compounded rectal suppository is administered rectally • Not recommended for acute treatment of seizures due to slower absorption rate
phenytoin[4,6]	No	• Limited evidence, unreliable results
topiramate[8]	Yes	• Similar rectal/oral absorption
valproic acid[16,23]	Yes	• Several studies demonstrate consistent rectal bioavailability/absorption • 1:1 (oral:rectal) dosing

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BENZODIAZEPINES				
Clonazepam (Klonopin)	Initial dosing: 0.5mg PO TID MDD: 20mg/day	Oral Disintegrating Tablet (ODT)*: 0.125mg, 0.25mg, 0.5mg, 1mg, 2mg Tablet: 0.5mg, 1mg, 2mg	• Long half-life • Broad spectrum • First line maintenance therapy • Can be used as a temporary measure to prevent or control seizures not managed by maintenance therapy • Titrate by 0.5-1mg/day every 3 days until response or as tolerated. • Usual maintenance dose is 2-8mg/day in 1-2 divided doses • Contraindicated if significant hepatic impairment	Y/N*
STEROIDS				
Dexamethasone	16-24mg daily in divided doses	Oral solution: 0.5mg/5ml, 1mg/ml Tablet: 0.5mg, 0.75mg, 1mg, 1.5mg, 2mg, 4mg, 6mg	• First line therapy for seizures due to brain tumors or brain metastases • Give last dose by 2pm to avoid steroid induced insomnia	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIEPILEPTICS				
Carbamazepine (Tegretol)	Initial (IR): 200mg BID Initial (ER): 200mg BID MDD (IR): 1,600mg/day divided BID-QID MDD (ER): 1,600mg/day divided BID	Capsule (ER)*: 100mg, 200mg, 300mg Chewable tablet: 100mg Oral suspension: 100mg/5ml Tablet: 200mg Tablet (ER)*: 200mg, 400mg	• Effective for partial and generalized tonic-clonic seizures • Titrate by 200mg/day per week until response or as tolerated • May induce own metabolism; loss of seizure control 2-4 weeks after starting may indicate this and need to increase dose • Takes 21-28 days to reach steady state due to enzyme auto-induction • GI side-effects may be minimized by taking with food or reducing the dose • Many drug interactions (enzyme inducer) • Goal serum levels: 4-12mcg/ml • Doses greater than 1,200mg typically not required • Patients of Asian descent are more likely to experience serious/potentially fatal adverse effect Stevens-Johnson syndrome or toxic epidermal necrolysis • Use with caution/ avoid if hepatic impairment • Adjust dose if ESRD • Small studies demonstrated that carbamazepine is effective and well-tolerated when administered rectally.[25,13]	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIEPILEPTICS (CONTINUED)				
Divalproex (Depakote)	Initial (DR forms): 10-15mg/kg/day (divided BID-TID if total daily dose exceeds 250mg) Initial (ER form): 10-15mg/kg/day QD MDD (all forms): 60mg/kg/day	Sprinkle capsule (DR): 125mg Tablet (DR)*: 125mg, 250mg, 500mg Tablet (ER)*: 250mg, 500mg	• First line maintenance therapy • Titrate by 5-10mg/kg per week until response or as tolerated • Broad spectrum agent that may be used as monotherapy or adjuvant • GI side effects are common, but tolerance usually develops within 1-2 weeks • Postural tremor is an extremely common adverse effect (up to 57% patients) • Contraindicated if significant liver disease • Sprinkle capsules may be opened and sprinkled on small amount of soft food • ER dosage form approximately 8-20% less bioavailable than DR forms; increase total daily dose by 8-20% if converting DR to ER; decrease by 8-20% if ER to DR.	Y/N*
Ethosuximide (Zarontin)	Initial: 250mg BID MDD: 1,500mg/day	Capsule: 250mg Syrup: 250mg/5ml	• Useful only for absence seizure • Divide doses to minimize GI side-effects, which are common • Titrate doses by 250mg/day every 4-7 days until response or as tolerated • May cause a number of psychological adverse effects, including aggressiveness, depression, paranoia • Expensive	Y
Felbamate (Felbatol)	Initial: 1,200mg/day divided TID-QID MDD: 3,600mg/day	Oral suspension: 600mg/5ml Tablet: 400mg, 600mg	• Adjunct for Lennox-Gastaut syndrome • Patient and prescriber must sign waiver/ risk acknowledgement form • Aplastic anemia is a serious potential adverse effect • Expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIEPILEPTICS (CONTINUED)				
Fosphenytoin (Cerebyx)	Initial: load with 10-20mg IV PE/kg at a rate not to exceed 150mg PE/minute, then 4-6mg PE/kg/day in divided doses MDD: based on serum concentrations	Solution for injection: 100mg PE /2ml	• 1mg PE (phenytoin equivalent) = 1.5mg Fosphenytoin • Not commonly used in the hospice setting	-
Gabapentin (Neurontin)	Initial: 300mg TID MDD: 3,600mg/day	Capsule: 100mg, 300mg, 400mg Solution: 250mg/5ml Tablet: 400mg, 600mg, 800mg	• Adjunct treatment for partial seizures • Usual effective dose for seizure is 900-1,800mg/day divided TID • Useful for neuropathic pain; not commonly used for seizure prevention • Reduce dose with renal impairment • Not absorbed rectally.[19]	Y
Lacosamide (Vimpat)	Initial (adjunct therapy): 50mg BID Initial (monotherapy): 100mg BID MDD: 400mg/day(300mg/day if significant renal or hepatic impairment)	Oral solution: 10mg/ml Solution for injection: 10mg/ml Tablet: 50mg, 100mg, 150mg, 200mg	• Effective for partial seizures • PO:IV is 1:1 • Titrate by 100mg/day per week until response or as tolerated • Reduce dose if renal impairment or mild to moderate hepatic impairment • Not recommended if severe hepatic impairment • Expensive	Y
Lamotrigine (Lamictal)	Initial: (see titration schedule, **Table 1**) MDD (monotherapy): 200mg/day MDD (valproate adjunct): 100mg/day MDD (enzyme-inducing antiepileptic adjunct): 400mg/day	Chewable tablet: 5mg, 25mg Tablet: 25mg, 100mg, 150mg, 200mg Tablet (ER)*: 25mg, 50mg, 100mg, 200mg, 250mg, 300mg	• Broad spectrum agent • Black box warning for rash: follow strict titration schedule • Titration may vary based on adjunct therapy if present as metabolism is subject to enzyme induction and inhibition • Reduce dose if moderate to severe hepatic impairment • Lamotrigine is absorbed rectally, though not to the same degree as it is orally; dose increases may be necessary if given by the rectal route.[1,2] • Expensive	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
		ANTIEPILEPTICS (CONTINUED)		
Levetiracetam (Keppra)	Initial: 500mg BID MDD: 3,000mg/day	Oral solution: 100mg/ml Solution for injection: 5mg/ml, 10mg/ml, 15mg/ml, 100mg/ml Tablet: 250mg, 500mg, 750mg, 1,000mg Tablet (ER): 500mg, 750mg	• Broad spectrum agent • Behavioral problems (including aggression, agitation, anger, anxiety and irritability) occur in about 10% of patients • Titrate by 1,000mg/day every 2 weeks until response or as tolerated • PO:IV is 1:1 • Undiluted IV doses of ≤1,000mg can be administered safely over 2 to 5 minutes[29] • Mixed evidence suggests that rectal administration with either tablets or oral solution is possible, although reduced blood levels have been reported and rectal bleeding is a possible adverse effect • Rectal absorption may be reduced by approximately 50%, so a 1:2 oral:rectal conversion ratio seems rational. • Requires renal dose adjustment with any level of renal impairment (starting at CrCl 80ml/min)	N
Oxcarbazepine (Trileptal)	Initial: 300mg BID (150mg BID if CrCl < 30ml/min) MDD: 2,400mg/day	Oral suspension: 300mg/5ml Tablet: 150mg, 300mg, 600mg Tablet (ER)*: 150mg, 300mg, 600mg	• Effective for partial and generalized tonic-clonic seizures • Better tolerated than carbamazepine • Fewer drug interactions than carbamazepine • Titrate by 300mg/day (adjunct therapy) or 600mg/day (monotherapy) per week until response or as tolerated • Reduce dose if renal impairment • Unlikely to reach sufficient therapeutic levels when administered rectally.[7]	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIEPILEPTICS (CONTINUED)				
Phenobarbital (Luminal)	Initial: 60-200mg QD or 100-300mg divided BID-TID or 1-3mg/kg/day divided QD-TID MDD: not established; determined by serum concentrations.	Elixir: 20mg/5ml Solution for injection: 65mg/ml, 130mg/ml Tablet: 7.5mg, 15mg, 16.2mg, 30mg, 32.4mg, 60mg, 64.8mg, 97.2mg, 100mg	• First line maintenance therapy • Useful for all types of seizure except absence • Signs of toxicity include: slowness, ataxia, nystagmus, coma • Consider bedtime dosing due to CNS effects • Consider monitoring serum levels to guide dosing, avoid toxicity • Wide therapeutic range: 15-40mg/L • Many drug interactions (enzyme inducer) • Will reduce efficacy of dexamethasone • Use with caution if hepatic impairment • Injection expensive • Total rectal absorption is comparable to the oral route when oral solution or compounded rectal suppository is administered rectally.[20] • Rectal route not recommended for acute treatment of seizures due to slower absorption rate.[20]	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIEPILEPTICS (CONTINUED)				
Phenytoin (Dilantin)	Initial (PO): 4-7mg/kg/day PO divided BID-TID (may administer ER forms QD-BID); may consider initial loading dose of 15-20mg/kg divided as three doses 2-4 hours apart. Initial (IV): 100mg IV Q6-8 hours MDD: not established; determined by serum concentrations. Usual maintenance doses range from 300-600mg/day.	Capsule (ER)*: 100mg, 200mg, 300mg Chewable tablet: 50mg Oral suspension: 100mg/4ml, 125mg/5ml Solution for injection: 50mg/ml	• Although first line maintenance therapy outside of the hospice setting, monitoring parameters may not be consistent with end of life care goals • Consider monitoring serum levels to guide dosing, avoid toxicity • Effective for partial, and generalized tonic-clonic seizures • Highly protein-bound, and increased effect expected with renal failure, hyperbilirubinemia, and hypoalbuminemia • Many drug interactions (enzyme inducer) • Will reduce efficacy of dexamethasone • Oral suspension binds to feeding tubes; enteral route not recommended. • IM route not recommended due to poor/ erratic absorption and adverse effects • Rectal administration is not recommended due to erratic and significantly reduced absorption • Therapeutic range: 10-20mg/L • Adverse effects associated with toxicity are concentration dependent: (20-30mg/L: nystagmus; 30-40mg/L: loss of coordination and seizure control; (>40mg/L): altered LOC / coma)	Y/N*
Pregabalin (Lyrica)	Initial: 150mg/day divided BID-TID MDD: 600mg/day	Capsule: 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg Oral solution: 20mg/ml	• Partial seizure adjunct therapy • Useful for neuropathic pain; not commonly used for seizure prevention • Expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIEPILEPTICS (CONTINUED)				
Primidone (Mysoline)	Initial: 100-125mg QHS MDD: 2,000mg/day	Tablet: 50mg, 250mg	• Also used at lower doses for treatment of essential tremor • Titrate by increasing dosing frequency from QD to BID, BID to TID, TID to QID every 3 days until response or as tolerated • Many drug interactions (enzyme inducer) • Therapeutic range: 8-12mcg/ml • Phenobarbital is an active metabolite; may also monitor phenobarbital level	Y
Tiagabine (Gabitril)	Initial: 4mg QD MDD: 56mg/day for patients receiving enzyme-inducing antiepileptics; lower if not.	Tablet: 2mg, 4mg, 12mg, 16mg	• Adjunct treatment for partial seizures • Titrate by increasing dosing frequency and dose as directed each week until response or as tolerated • Should be taken with food • Expensive	Y
Topiramate (Topamax, Qudexy XR, Trokendi XR)	Initial (IR): 25mg BID Initial (ER): 50mg QD MDD (all forms): 400mg/day	Capsule (ER)*: 25mg, 50mg, 100mg, 200mg Sprinkle capsule: 15mg, 25mg Sprinkle capsule (ER): 25mg, 50mg, 100mg, 150mg, 200mg Tablet*: 25mg, 50mg, 100mg, 200mg	• Broad spectrum agent • Monotherapy: titrate by 50mg/day per week until 200mg/day, then by 100mg/day per week until 400mg/day until response or as tolerated • Adjunct therapy: titrate by 25-50mg/day per week until response or as tolerated • Recommended titration varies depending on use as adjunct or monotherapy • May open ER capsule, but contents should not be crushed or chewed • Reduce dose if renal impairment • Adverse effects include weight loss and kidney stones • Rectal absorption is comparable to the oral route when tablets or suspension prepared from tablets is administered rectally.[8] • Expensive	Y/N*

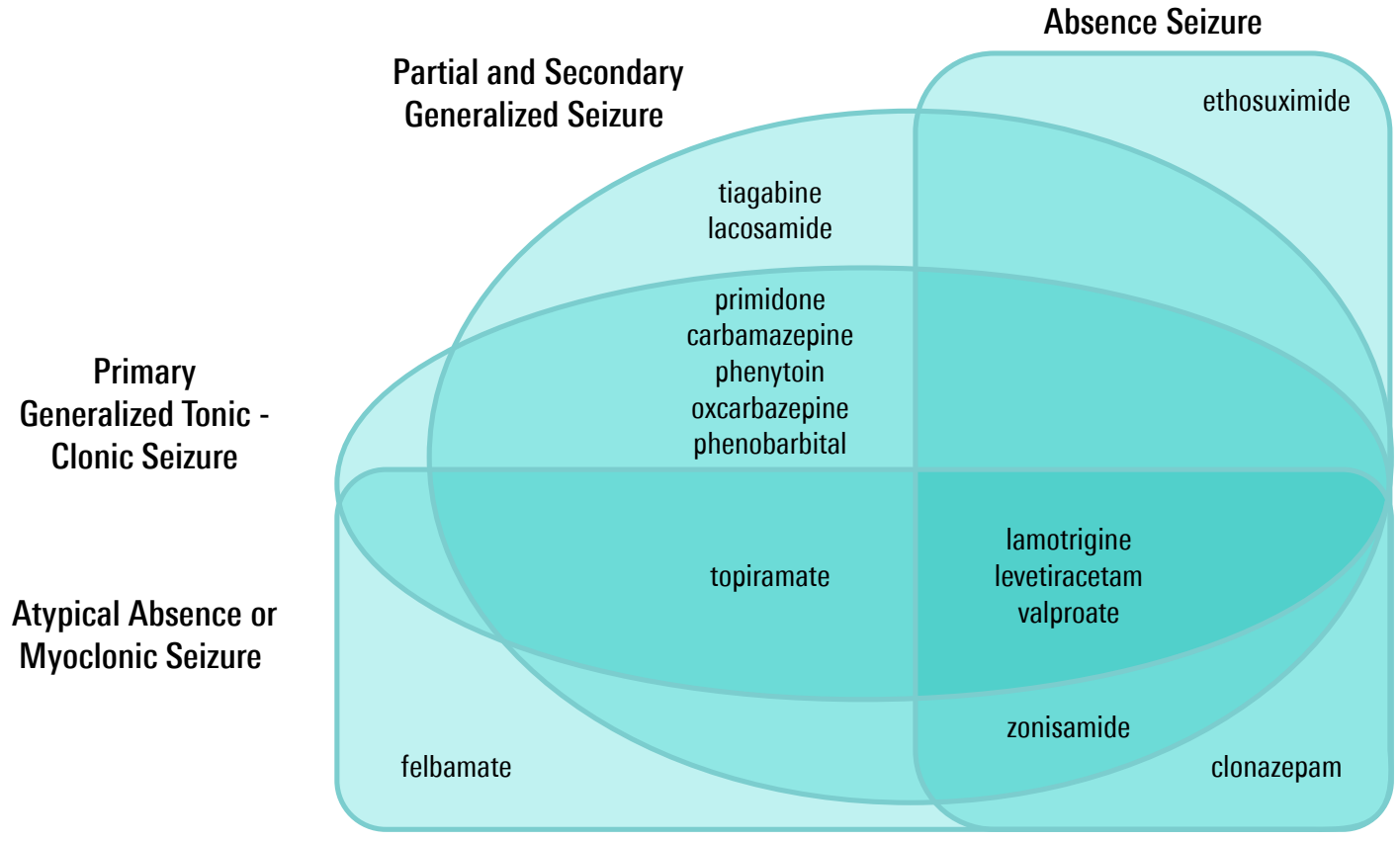
GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIEPILEPTICS (CONTINUED)				
Valproic Acid (Depakene)	Initial (PO): 10-15mg/kg/day (divided BID-TID if total daily dose exceeds 250mg) Initial (SQ): New valproic acid use / not converting from oral valproic acid: 25mg/hr (600mg/24 hours) by continuous SQ infusion; If previously maintained on valproic acid or divalproex, convert from oral to SQ at a 1:1 ratio and divide total daily amount by 24 for hourly rate. Sterile water for injection or normal saline can be used with infusion. MDD (PO): 60mg/kg/day MDD (SQ): not established for this route of administration	Capsule: 250mg Injection: 100mg/ml Oral Solution: 250mg/5ml	• First line maintenance therapy • Titrate by 5-10mg/kg per week until response or as tolerated • Broad spectrum agent that may be used as monotherapy or adjuvant • Tolerance to GI side effects develops within 1-2 weeks • Postural tremor is a common adverse effect • Contraindicated if significant liver disease • Approximately 1:1 conversion between valproic acid and divalproex DR • Continuous SQ infusion can be considered if the oral route is unavailable and may cause less sedation than alternate non-oral options for seizure suppression like benzodiazepines or barbiturates. • Rectal administration can be considered if the oral route is unavailable. Available data suggests to use a 1:1 oral:rectal conversion ratio. Valproic acid can be compounded as rectal suppositories or the oral solution can be administered rectally.	N
Zonisamide (Zonegran)	Initial: 100mg QD MDD: 600mg/day (doses greater than 400mg/day rarely more effective)	Capsule: 25mg, 50mg, 100mg	• Adjunct therapy in adults with partial seizures • Contraindicated if sulfonamide allergy • Titrate by 100mg/day every 2 weeks until response or as tolerated • Adverse effects include kidney stones and psychosis	N

QUICK REFERENCES

TABLE 1 – LAMOTRIGINE TITRATION SCHEDULE

	FOR PATIENTS TAKING VALPROATE	FOR PATIENTS NOT TAKING CARBAMAZEPINE, PHENYTOIN, PHENOBARBITAL, PRIMIDONE, OR VALPROATE	FOR PATIENTS TAKING CARBAMAZEPINE, PHENYTOIN, PHENOBARBITAL, OR PRIMIDONE AND NOT TAKING VALPROATE
Weeks 1 and 2	25mg every other day	25mg daily	50mg daily
Weeks 3 and 4	25mg daily	50mg daily	100mg daily divided BID
Week 5 and Onward	Increase by 25-50mg/day every 1-2 weeks	Increase by 50mg/day every 1-2 weeks	Increase by 100mg/day every 1-2 weeks
Usual Maintenance Doses	100-200mg/day with valproate alone 100-400mg/day with valproate and other drugs that induce glucuronidation (divided QD – BID)	225-375mg/day divided BID	300-500mg/day divided BID

FIGURE 1 – VENN DIAGRAM OF ANTIEPILEPTICS AND TYPE(S) OF SEIZURE TREATED



References

1. Birnbaum, A. K., Kriel, R. L., Burkhardt, R. T., & Remmel, R. P. (2000). Rectal absorption of lamotrigine compressed tablets. *Epilepsia, 41*(7), 850-853.
2. Birnbaum, A. K., Kriel, R. L., Im, Y., & Remmel, R. P. (2001). Relative bioavailability of lamotrigine chewable dispersible tablets administered rectally. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 21*(2), 158-162.
3. Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 841-8.
4. Burstein, A. H., Fisher, K. M., McPherson, M. L., & Roby, C. A. (2000). Absorption of phenytoin from rectal suppositories formulated with a polyethylene glycol base. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 20*(5), 562-567.
5. Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 352-356.
6. Chang, S. W., da Silva, J. H., & Kuhl, D. R. (1999). Absorption of rectally administered phenytoin: a pilot study. *Annals of Pharmacotherapy, 33*(7-8), 781-786.
7. Clemens, P. L., Cloyd, J. C., Kriel, R. L., & Remmel, R. P. (2007). Relative bioavailability, metabolism and tolerability of rectally administered oxcarbazepine suspension. *Clinical drug investigation, 27*(4), 243-250.
8. Conway, J. M., Birnbaum, A. K., Kriel, R. L., & Cloyd, J. C. (2003). Relative bioavailability of topiramate administered rectally. *Epilepsy research, 54*(2-3), 91-96.
9. Dunteman E. Levetiracetam administered by the rectal route is effective in treating neuropathic pain. [Abstract 766]. Presented at the Second Joint Scientific Meeting of the American Pain Society and Canadian Pain Society. May 6-9, 2004. Vancouver, Canada. Per manufacturer inquiry, January 2015.
10. Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 144.
11. Gallentine WB, Hunnicutt AS, Husain AM. Levetiracetam use in children with refractory status epilepticus. Epilepsia. 2007; 48(Suppl 6):356-357. [Abstract 3.294] Presented at: American Epilepsy Society Annual Meeting, Nove 30 – Dec 4, 2007. Philadelphia, PA, USA.
12. Graves NM, Kriel RL. Rectal administration of antiepileptic drugs in children. Pediatr Neurol. 1987;3:321-6.
13. Graves, N. M., Kriel, R. L., Jones-Saete, C., & Cloyd, J. C. (1985). Relative bioavailability of rectally administered carbamazepine suspension in humans. *Epilepsia, 26*(5), 429-433.
14. Gustafson MC, Penovich PE, Frost MD. Levetiracetam absorption after rectal administration: 2 case reports. *Epilepsia.* 2005; 46(Suppl 8):211. [Abstract 2.357] Presented at: American Epilepsy Society Annual Meeting, Dec 2-5, 2005. Washington, USA.
15. Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 1037-40, 1175-6, 1378, 1212.
16. Holmes, G. B., Rosenfeld, W. E., Graves, N. M., Remmel, R. P., Carlson, G. H., & Kriel, R. D. (1989). Absorption of valproic acid suppositories in human volunteers. *Archives of neurology, 46*(8), 906-909.
17. Kalra AA. Treatment of neonatal seizures with rectal levetiracetam. Epilepsia. 2005; 46(Suppl 8):196. [Abstract 2.313] Presented at: American Epilepsy Society Annual Meeting, Dec 2-5, 2005.
18. Kanazawa O, Sengoku A, Kawai I. Treatment of childhood epilepsy with rectal valproate: case reports and pharmacokinetic study. Brain Dev. 1987;9:615-20.
19. Kriel, R. L., Birnbaum, A. K., Cloyd, J. C., Ricker, B. J., Saete, C. J., & Caruso, K. J. (1997). Failure of absorption of gabapentin after rectal administration. *Epilepsia, 38*(11), 1242-1244.
20. Leppik, I. E., & Patel, S. I. (2015). Intramuscular and rectal therapies of acute seizures. *Epilepsy & Behavior, 49*, 307-312.
21. Lexi-comp 5-min. consults: Seizure disorder, Seizure disorder (absence), Seizure disorder (Partial).
22. Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
23. Moolenaar, F., Greving, W. J., & Huizinga, T. (1980). Absorption rate and bioavailability of valproic acid and its sodium salt from rectal dosage forms. *European journal of clinical pharmacology, 17*(4), 309-315.
24. O'Connor, N. Sodium valproate as a continuous subcutaneous infusion: A case series, JPSM, 2017; article in press.
25. Patel, V., Cordato, D. J., Malkan, A., & Beran, R. G. (2014). Rectal carbamazepine as effective long-acting treatment after cluster seizures and status epilepticus. *Epilepsy & Behavior, 31*, 31-33.
26. Schachter, S. et al. Overview of the management of epilepsy in adults, UpToDate, literature review current through Nov. 2015.
27. Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 644-669.
28. Yoshiyama Y, Nakano S, Ogawa N. Chronopharmacokinetic study of valproic acid in man: comparison of oral and rectal administration. J Clin Pharmacol. 1989; 29:1048-52.
29. Morgan O, et al. Safety and tolerability of rapid administration undiluted levetiracetam. Neurocritical Care. 2020;32:131–134.

Seizures (Status Epilepticus)

DEFINITION

Seizure: the clinical manifestation of an abnormal, excessive, hyper-synchronous discharge of a population of cortical neurons.

Status epilepticus: a state of medical emergency characterized by seizure lasting more than 5 minutes or two or more seizures that occur without complete recovery of consciousness between them.

CAUSES

- Brain tumors / metastases
- Head injury/trauma
- Stroke/TIA
- Infection
- Fever
- Hypoglycemia
- Metabolic disturbances
- Hypoxia
- Sleep deprivation
- Encephalopathy
- Drug withdrawal/abrupt discontinuation (eg., anticonvulsants, benzodiazepines, opioids, sedatives, alcohol)
- Medications (eg., bupropion, tramadol, meperidine, fluroquinolone and cephalosporin antibiotics, antipsychotics, other antidepressants, severe phenytoin toxicity)

HOW TO RECOGNIZE SYMPTOM

- Patient has been seizing for a prolonged period of time (>5 minutes) or incomplete recovery between seizures
- Impaired consciousness
- Confusion
- Muscle stiffness
- Rhythmic jerking of extremities
- Bowel/bladder incontinence
- Respiratory compromise

CLINICAL INSIGHTS

- Exclude hypoglycemia as cause of seizure
- Non-pharmacological
  - » Remove objects around the patient to reduce likelihood of injury
  - » Do not try to move the patient or put anything in their mouth (with the exception of buccal midazolam) while they are seizing
  - » If possible, turn the patient onto their side to prevent them from injury or aspiration
- Regarding the decision to medicate during acute seizure:
  - » Although most seizures self-terminate, the probability of self-termination without medication drops considerably in seizures lasting longer than 2 minutes.
  - » The longer the duration of status epilepticus prior to administration of medications, the lower the chances of successful seizure control with pharmacotherapy.
  - » Because it is unknown how long a seizure will last, it is reasonable to treat acute seizures as promptly as possible prior to the development of status epilepticus
- Although prophylaxis with antiepileptics is not typically recommended in patients with brain tumors who have not had a previous seizure, preparing for the possibility of seizure by having medication on hand for acute treatment is reasonable due to the high incidence of seizure in this population.
  - » Incidence of seizure for patients with brain tumors or cerebral metastases is estimated to be between 20-50%
  - » Slow growing tumors, such as low grade astrocytomas, oligodendrogliomas, gangliomas and dysembryoplastic neuroepithilial tumors are more likely to induce seizures.
- Oral drug therapy is not recommended as loading regimens are generally not tolerated and time to therapeutic levels may take several days.
- Consider providing an on-demand peripheral IV access site for a patient with recurrent seizures
- Benzodiazepines, including lorazepam, diazepam and midazolam are first line therapies. Buccal midazolam

is first line therapy when the parenteral route is unavailable or impractical. Rectal diazepam (with gel or solution for injection) or intranasal midazolam may also be considered.

  - » Although commonly used in the hospice setting, clinical evidence does not support the use of rectal diazepam suppositories or sublingual lorazepam.

- Durations of actions of benzodiazepines for seizure control do not correlate with their pharmacological half-lives and may be shorter (as with diazepam) or longer (as with lorazepam) than predicted.
- No ceiling dose exists for benzodiazepines used to control acute seizures
- Benzodiazepine resistant status epilepticus may require treatment with second or third line parenteral agents, such as phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or lacosamide.
- Refractory status epilepticus (lasting >60 minutes) may require palliative sedation or general anesthesia with midazolam, propofol or phenobarbital (**Table 1**).

TABLE 1 – DRUG SELECTION ALGORITHM FOR TREATMENT OF STATUS EPILEPTICUS

MINUTES SINCE ONSET OF SE	TREATMENT
0	Stabilize patient (ie, airway, breathing and circulation)
> 5	IV lorazepam or IV/SQ/IM/buccal/intranasal midazolam or IV/PR diazepam Then: IV valproic acid or IV phenytoin Then: IV phenobarbital
> 60 (refractory SE)	IV propofol and/or IV pentobarbital

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Diazepam (Valium)	Initial (IV): 0.1-0.3mg/kg up to 20mg max IV infused at a rate not to exceed 5mg/min; may repeat in 15min Initial (PR): 0.2-0.5mg/kg up to 20mg max of rectal gel or solution for injection given with plastic syringe and catheter; may repeat up to 10mg in 10 minutes if needed MDD: no definitive max dose; clinicians should be guided by effect/ seizure control	Rectal gel: 2.5mg, 10mg, 20mg Solution for injection: 5mg/ml	• Benzodiazepine of choice for PR route although studies of diazepam suppositories have demonstrated erratic and low plasma concentrations; this dosage form of diazepam is not recommended for emergency treatment • Not first line therapy for IV route • Rapid onset, but 50% incidence of seizure recurrence within 2 hours after administration if no other AED given due to redistribution into adipose tissue • Shortest duration of action of benzodiazepines recommended for acute seizure: (<2 hours)	Y
Lorazepam (Ativan)	Initial (IV, SQ): 0.1mg/kg or 4mg max at a rate not to exceed 2mg/min (typical dose 4mg); may repeat in 20 minutes if needed MDD: no definitive max dose; clinicians should be guided by effect/ seizure control	Solution for injection: 2mg/ml, 4mg/ml	• Benzodiazepine of choice for IV route • Well absorbed SL, but there is only limited, mainly anecdotal evidence of its use sublingually for acute seizure. The sublingual route is often not available during seizure due to clenched jaw/teeth. Additionally, the dose may inadvertently be swallowed, resulting in delayed onset of action. • Avoid rectal administration due to reduced efficacy and increased time to onset • Duration of action of seizure control is up to 72 hours with parenteral administration	Y
Midazolam (Versed)	Initial (IV, SQ): 0.15-0.3mg/kg up to max of 15mg repeated every 10-15min as needed Initial (IM, intranasal, buccal): 10mg if weight > 40kg; 5mg if weight < 40kg MDD: no definitive max dose; clinicians should be guided by effect/ seizure control	Solution for injection: 1mg/ml, 5mg/ml Syrup: 2mg/ml	• Benzodiazepine of choice for IM, buccal route, intranasal • Intranasal route requires specialized atomizer to be used with solution for injection • Duration of action of seizure control is about 3-4 hours • May be given via continuous infusion for refractory status epilepticus • Solution for injection can be given bucally in place of oral solution to reduce volume per dose	-

References

- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 845-7.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 355-356.
- Drislane, F. et al. Convulsive status epilepticus in adults: Treatment and prognosis, UpToDate.com, accessed online 7/23/15.
- Fast Fact #229 Seizure Management In The Dying Patient – accessed online www.capc.org
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 144.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 1040-2, 1175, 1344-5.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Mazurkiewicz-Beldzinska, M. et al. Current treatment of convulsive status epilepticus – a therapeutic protocol and review, Anaesthesiology Intensive Therapy, 2014, Vol. 46 No.4, 293-300.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 333.
- Rey, E. et al. Pharmacokinetic Optimisation of Benzodiazepine Therapy for Acute Seizures – Focus on Delivery Routes, Clinical Pharmacokinetics, 1999 June; 36(6): 409-424.
- Rogalski, R. et al. Benzodiazepine Selection in the Management of Status Epilepticus – A Review, Advanced Emergency Nursing Journal, Vol.37, No.2, pp. 83-94.
- Status Epilepticus in a Hospice Inpatient Setting, Journal of Pain and Symptom Management, Vol.36 No.1 July 2008.
- Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 715-724.

Urinary Symptoms

(Incontinence, Bladder Spasms, Urinary Retention, Dysuria)

DEFINITIONS

Incontinence is the weakening of the pelvic floor muscles leading to poor control of urination and defecation

- Incontinence is commonly attributable to multiple mechanisms
- Different types of urinary incontinence include: stress, urge, mixed, reflex, overflow, and functional. The underlying pathology and symptoms may present differently based upon the type of incontinence observed
- Fecal incontinence occurs when the normal anatomy and/or physiology that maintains the structure and function of the anorectal area is disrupted. The internal anal sphincter provides most of the resting anal pressure and is reinforced during voluntary squeeze by the external anal sphincter, the anal mucosal folds, and the anal endovascular cushions. Disruption or weakness of the external sphincter can cause urge-related or diarrhea-associated fecal incontinence.

Bladder spams occur when the bladder muscle squeezes suddenly causing an urgent need to release urine.

- Involuntary muscle contractions can cause an inability to control the voiding of urine which can lead to leaking, pain, and incontinence.
- They are a common cause of overactive bladder and urge incontinence
- Spasms can be associated with changes in blood supply and/or function of the nerves controlling the bladder

Urinary retention is the inability to empty the bladder resulting in residual urine following voiding.

- It can be acute or chronic:
  - » Acute urinary retention: patient cannot urinate, can cause severe pain and discomfort
  - » Chronic urinary retention: patient can urinate, however, they do not empty the urine from the bladder completely. Patient's may not realize they have this condition until another condition develops (urinary incontinence or infection)

Dysuria is painful urination described as burning sensation or discomfort.

- This typically is the result of bladder or urethra irritation that could cause difficulty initiating urination and burning during urination

CAUSES

- Incontinence:
  - » Bladder (urge and overflow) or urethral (stress) dysfunction
  - » **DRIP**
    - ° **D**elirium/**D**rugs, **R**estricted mobility, **I**nfection/**I**mpaction, **P**olyuria
  - » **DIAPPERS**
    - ° **D**elirium, **I**nfection, **A**trophic urethritis, **P**sychological disorders, **P**harmacy, **E**xcess urine production, **R**estricted mobility, **S**tool impaction
  - » Medications:
    - ° Alcohol, alpha adrenergic agonists (pseudoephedrine), alpha blockers (doxazosin, terazosin, tamsulosin), angiotensin-converting enzyme (ACE) – inhibitors, anticholinergics, antidepressants (amitriptyline, nortriptyline), antihistamines (diphenhydramine), antipsychotics (haloperidol, risperidone), caffeine, calcium channel blockers, diuretics (furosemide, thiazides), opioids, sedatives (diazepam, lorazepam)
  - » Overflow:
    - ° Over distended bladder due to obstruction (eg, prostate cancer, BPH)
    - ° Reduction or absence of bladder contractions
    - ° Medications causing urinary retention
  - » Stress:
    - ° Weak pelvic floor muscles
    - ° Weakened sphincter muscle
  - » Urge:
    - ° Detrusor muscle over activity (overactive bladder)
    - ° May be associated with outflow obstruction (tumor) or CNS disorder (stroke, dementia)
  - » Functional:

- Immobility
- Dementia or neurologic or psychological disorders (eg, depression)

» Trauma
» Age
» Heavy activity
» Overweight
» Pelvic malignancy
» Renal disease
» Smoking

- Bladder spasm:
  - » Age
  - » Bladder injury
    - Distension
    - Infection
    - Obstruction
      - › Bladder stones, polyps, or cancer (tumor)
      - › Enlarged prostate
    - Nerve damage
      - › Diabetes, stroke, multiple sclerosis, brain/spinal cord injuries
  - » Medications:
    - Bethancehol, diuretics
  - » Food/drinks
    - Alcohol, caffeinated beverages, chocolate, citrus fruits
  - » Neuromuscular disease (eg,: Parkinson)
  - » Indwelling urinary catheter
  - » Abdominal, bladder, or pelvic surgery
  - » Changes in blood supply
- Urinary retention
  - » Medications
    - Alpha adrenergic agonists, antihistamines, anticholinergics, antidepressants, antiparkinson agents, antispasmodics, antipsychotics NSAIDS, opioids, sedatives (diazepam), calcium channel blockers (nifedipine), carbamazepine, cyclobenzaprine
  - » Obstruction causing decreased urine flow
    - Enlarged prostate, urethral stricture, bladder/urinary tract stones, cancer/tumors, constipation, cystocele, rectocele
  - » Nerve damage
    - Diabetes, stroke, multiple sclerosis, brain/spinal cord injuries
  - » Weakened bladder muscles:
    - Aging, women with multiple (vaginal) child births, pelvic trauma
  - » Neuromuscular disease (eg, Parkinson)
  - » Local inflammation
  - » Complication of indwelling catheter removal
- Dysuria
  - » Infection/inflammation – cystitis, pyelonephritis, urethritis, prostatitis, atrophic vaginitis
    - Most common organism: *Escherichia coli, staphylococcus, Klebsiella sp., Proteus sp.*
  - » Trauma
    - Catheter placement
  - » Neoplasm/tumors
    - Bladder, prostate, renal cell, vaginal, penile
  - » Bladder neck obstruction (benign prostate hypertrophy)
  - » Urethral strictures
  - » Endometriosis

HOW TO RECOGNIZE SYMPTOM

- Incontinence:
  - » Inability to hold urine or feces
  - » Overflow
    - Leakage of small amount of urine due to over distended bladder
    - Dysuria, hesitancy, frequency, incomplete voiding, weak stream
  - » Stress
    - Leakage of small amount of urine with exertion
    - Leakage associated with increased abdominal pressure from laughing, sneezing, coughing, climbing stairs, or other physical stressors on the abdominal area
  - » Urge
    - Involuntary leakage of large amount of urine, accompanied by or immediately preceded by urgency
    - Frequency, nocturia

  - » Functional
    - ° Leakage of urine due to patient's inability to reach toilet due to inability to recognize the need to urinate or defecate, lack of desire, lack of ability to communicate, or environmental barriers
  - » Mixed
    - ° Combination of two incontinences, usually urge and stress
- Bladder Spasms:
  - » Urinary frequency and urgency to void; feeling is often more intense
  - » Dysuria
  - » Inability to initiate urinary stream
  - » Colicky pain or burning in lower pelvis
- Urinary Retention:
  - » Acute:
    - ° Inability to urinate, discomfort or pain, frequent urge to urinate, bloating
  - » Chronic:
    - ° Urinary frequency and urgency, difficulty starting a stream of urine, weak urine flow, bladder feels full after urination, dribbling between trips to the toilet, discomfort in lower abdomen and urinary tract
- Dysuria
  - » Uncomfortable or painful urination
  - » Sharp or burning sensation
  - » Ache over bladder
  - » Flank pain
  - » Hematuria
  - » Men: penile discharge, scrotal pain, perineal pain
  - » Women: vaginal discharge
  - » Urinary tract symptoms
    - ° Bladder irritation: urinary frequency, urgency
    - ° Obstruction: hesitancy, weak stream, dribbling
  - » Urinary tract infection symptoms:
    - ° Fever, cloudy urine
  - » Trauma:
    - ° Recent history of cystoscopy, catheterization, or surgery

CLINICAL INSIGHTS

- Evaluate the effectiveness of the medication and if the symptoms persist and therapy is ineffective, consider discontinuation
- For individuals with a decompensated bladder that does not empty well, the post-void residual urine can lead to overgrowth of bacteria causing a UTI (urinary tract infection); monitor patient for signs and symptoms of infection
- If patient has symptoms of UTI, it may be helpful to obtain a urinalysis to rule out infection or to treat empirically with antibiotics
- Incontinence:
  - » Evaluate the symptoms and potential causes to help guide therapy.
  - » Anticholinergic medications that are used for urinary incontinence commonly cause many adverse reactions such as: dry mouth, confusion, constipation and tachycardia. Monitor closely for adverse effects with use and consider the possibility of adverse effects when initiating or titrating therapy
  - » Without effective treatment, urinary incontinence is associated with unfavorable outcomes including: contact dermatitis, skin breakdown, pressure sores and ulcers
  - » Catheterization may be considered after other treatment options have been eliminated
- Bladder spams:
  - » Anticholinergic medications that are used for urinary incontinence commonly cause many adverse reactions such as: dry mouth, confusion, constipation and tachycardia. Monitor closely for adverse effects with use and consider the possibility of adverse effects when initiating or titrating therapy
  - » If patient has indwelling catheter, ensure it is functioning properly. If needed, consider irrigation or replacement.
- Urinary retention
  - » More common in men than women
  - » If possible, consider discontinuation/dose reduction of medications known to cause/exacerbate urinary retention

- » Acute: insertion of a catheter may be beneficial; reevaluate continued need after initial relief due to increased risk of infection
- » Chronic: intermittent catheterization may be needed; if other treatments fail, long-term catheterization may be required
- » Urethral dilation and stents are other interventional therapies that may be considered

- Dysuria
  - » If possible, identify and treat the underlying cause(s)
- There are receptors sites on the bladder and sphincter that relax or contract the bladder or sphincter. Since several medication classes target these bladder or receptor sites, the specific indications for the medications may overlap

TABLE 1

MEDICATION CLASSES	INCONTINENCE	BLADDER SPASMS	URINARY RETENTION	DYSURIA
Anticholinergic	X	X*		
Antidepressants	X (Stress)			
Alpha Agonists (Pseudoephedrine)	X (Stress)			
Beta Agonist (Mirabegron)	X (Urge)			
Cholinergic Agonist (Bethanechol)	X (Overflow)		X	
Antispasmodics	X* (Urge)	X		
Alpha Adrenergic Receptor Blockers			X	
Urinary Analgesics				X

*Only certain medications in class can be used (see table below)

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICHOLINERGIC				
Darifenacin (Enablex)	Initial: 7.5-15mg Daily MDD: 15mg/day (7.5mg/day when used with potent CYP3A4 inhibitors)	Tablet (ER): 7.5mg, 15mg	• Urinary incontinence, overactive bladder • Less anticholinergic than oxybutynin • MDD is 7.5mg if concurrent CYP3A4 inhibitors (eg, clarithromycin, ketoconazole, nefazodone, grapefruit) • Expensive	N
Dicyclomine (Bentyl)	Initial: 10-20mg PO QID MDD: 160mg/day	Capsule: 10mg Syrup: 10mg/5ml Tablet: 20mg	• Urinary incontinence • Safety data unavailable for doses > 80mg/day for durations > 2 weeks	Y
Fesoterodine (Toviaz®)	Initial: 4mg PO QD MDD: 8mg/day	Tablet: 4mg, 8mg	• Urinary incontinence, overactive bladder • Prodrug to tolterodine • MDD 4mg/day for renal impairment • Many drug interactions (CYP3A4 substrate)	N
Hyoscyamine (Levsin, Symax, Anaspaz)	Initial (IR): 0.125-0.25mg PO/SL q4h Initial (ER): 0.375-0.75mg PO q12h MDD: 1.5mg/day	Elixir: 0.125mg/5ml Oral solution: 0.125mg/ml Oral disintegrating tablet (ODT): 0.125mg Solution for injection: 0.5mg/ml Tablet: 0.125mg, 0.15mg Tablet (SL): 0.125mg Tablet (ER)*: 0.375mg	• Urinary incontinence • Antacid may interfere with absorption • Active isomer of atropine	Y/N*
Oxybutynin (Ditropan, Gelnique, Ditropan XL, Oxytrol)	Initial (IR): 2.5-5mg PO BID-TID Initial (ER): 5mg PO QD Initial (Gel): 3 pumps or 1 sachet topically QD Initial (Patch): 1 patch topically changed twice weekly MDD (IR): 20mg/day MDD (ER): 30mg/day MDD (Transdermal): Same as initial	Gel: 10% Patch: 3.9mg/ 24 hr Syrup: 5mg/5ml Tablet: 5mg Tablet (ER)*: 5mg, 10mg, 15mg	• Urinary incontinence, antispasmodic effect • Geriatric patients: start with 2.5mg BID • Monitor for anticholinergic side effects • Gel is flammable; avoid smoking after application • IR tablets, syrup are most cost effective *(Continued on next page)*	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICHOLINERGIC (CONTINUED)				
Propantheline (Pro-Banthine®)	Initial: 7.5mg PO QD - 15mg QID (AC, HS) MDD: 360mg/day	Tablet: 15mg	• Urinary incontinence; antispasmodic effects • Requires frequent dosing • Administer 30min before meals • Titrate to response as tolerated • Side effects include constipation, chest pain, fever and dry mouth	Y
Solifenacin (Vesicare)	Initial: 5mg PO QD MDD: 10mg/day (5mg/day if CrCl < 30ml/min)	Tablet: 5mg. 10mg	• Urinary incontinence, overactive bladder • Less anticholinergic than oxybutynin • May cause QT-interval prolongation • Requires renal dose adjustments • Expensive	N
Tolterodine (Detrol, Detrol LA)	Initial (IR): 2mg PO BID Initial (ER): 4mg PO QD MDD (IR, ER): 4mg/day (2mg/day if hepatic impairment or CrCl 10-30 ml/min)	Tablet: 1mg, 2mg Tablet (ER)*: 2mg, 4mg	• Urinary incontinence, overactive bladder • Initial dose may be halved based on response and tolerability • Less anticholinergic than oxybutynin • Severe hepatic impairment or CrCl < 10ml/min: not recommended • Drug interactions with azole antifungals, fluoxetine, macrolide antibiotics	Y/N*
Trospium (Sanctura, Sanctura XR)	Initial (IR): 20mg PO QD-BID Initial (ER): 60mg PO QAM MDD (IR): 40mg/day MDD (ER): 60mg/day	Tablet: 20mg Tablet (ER)*: 60mg	• Geriatric patients: start with QHS dosing • Urinary incontinence, overactive bladder • Less risk of confusion (does not cross BBB) • Does not cause drug-drug interactions • Expensive	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIDEPRESSANTS				
Amitriptyline (Elavil)	Initial: 10mg PO at bedtime MDD: 300mg/day	Tablet: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	• Urinary incontinence • TCA • Benefit due to antimuscarinic effect, other TCAs not substitutable • May increase dose by 25mg every 1-2 weeks (effective dose is typically > 50mg) • May also help with sleep, mood, neuropathic pain • Increases risk of falls	Y
Duloxetine (Cymbalta®)	Initial: 20mg PO BID MDD: 80mg/day	Capsule (DR): 20mg, 30mg, 60mg	• Stress Incontinence • SNRI • Increases urinary sphincter muscle tone • Adverse effects include: nausea, headache, drowsiness, fatigue • Not recommended if CrCl < 30ml/min • Capsules may be opened and sprinkled onto apple sauce and swallowed immediately. Do not use chocolate pudding • Benefits within 2 weeks of initiation • After 2 weeks, slowly titrate to a target of 40mg BID • Expensive	N
Imipramine (Tofranil)	Initial: 25mg PO QHS MDD: 150mg/day (100mg/dayingeriatric patients)	Capsule: 75mg, 100mg, 125mg, 150mg Tablet: 10mg, 25mg, 50mg	• Urinary incontinence • TCA • Benefit due to antimuscarinic effect, other TCAs not substitutable • Gradually titrate dose to response or until adverse effects become intolerable • Avoid use of MAO inhibitors	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ALPHA AGONIST				
Pseudoephedrine (Sudafed®)	Initial: 30-60mg PO Q6 hours MDD: 120mg/day	Oral solution: 15mg/5ml, 30mg/5ml Tablet: 30mg, 60mg Tablet (ER, 12 hour)*: 120mg Tablet (ER, 24 hour)*: 240mg	• Stress incontinence (not FDA approved for this indication) • Adverse effects include: insomnia, anxiety • Not recommended in patients with cardiovascular disease, BPH, glaucoma, DM • Can cause urinary retention	Y/N*
BETA AGONISTS				
Mirabegron (Myrbetriq)	Initial: 25mg PO QD MDD: 50mg/day (25mg/day if CrCl 15-29ml/min)	Tablet (ER): 25mg, 50mg	• Urinary Incontinence, Overactive Bladder • Beta-3 agonist • Requires renal dose adjustment • Avoid if CrCl < 15ml/min • Lacks anticholinergic effects • Adverse effects include HTN, nasopharyngitis, UTI, headache • Avoid in patients with cardiovascular disease • Expensive	N
Terbutaline (Brethine®)	Initial: 2.5mg-5mg PO TID MDD: 15mg/day	Solution for injection: 1mg/ml Tablet: 2.5mg,5mg	• Urinary incontinence • Beta-2 agonist that helps relax bladder • Adverse effects include tachycardia, nervousness, dizziness and nausea/vomiting • Requires renal dose reduction; decrease dose by 50% if CrCl 10-50ml/min; avoid if < 10ml/min	Y
CHOLINERGIC AGONIST				
Bethanechol (Urecholine®)	Initial: 10-50mg PO 3-4x/day MDD: 200mg/day	Tablet: 5mg, 10mg, 25mg, 50mg	• Overflow incontinence; urinary retention • Cholinergic agonist; helps increase bladder muscle tone causing contraction and initiation of urination • Adverse effects include: hypotension, diaphoresis, tachycardia, headache, urinary urgency • Take 1 hour before or 2 hours after meal	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTISPAMODICS				
Belladonna/Opium (B&O suppository)	Initial: 0.5-1 suppository PR QD - BID MDD: 4 suppositories/ day	Suppository: 16.2/30mg, 16.2/60mg	• Bladder spasms • Useful if patient is unable to tolerate oral medications • Expensive	-
Flavoxate (Urispas)	Initial: 100-200mg PO TID-QID MDD: 800mg/day	Tablet: 100mg	• Bladder spasms; urinary incontinence • Consider for elderly patients who suffer from anticholinergic side effects from other medications • Reduce dose once symptoms improve	Y
ALPHA ADRENERGIC RECEPTOR BLOCKERS				
Alfuzosin (Uroxatral®)	Initial: 10mg PO QD MDD: 10mg/day	Tablet (ER): 10mg	• Urinary retention; urge or overflow incontinence associated with BPH • Adverse effects include: Upper respiratory tract infection/bronchitis	N
Doxazosin (Cardura®, Cardura XL®)	Initial: 1-2mg PO QD MDD: 8mg/day	Tablet: 1mg, 2mg, 4mg, 8mg Tablet (ER)*: 4mg, 8mg	• Urinary retention; urge or overflow incontinence associated with BPH • Helps to relax bladder and allow emptying • Often used for treatment of hypertension • Adverse effects include: Edema, orthostatic hypotension	Y/N*
Silodosin (Rapaflo®)	Initial: 8mg PO QD MDD: 8mg/day	Capsule: 4mg, 8mg	• Urinary retention; urge or overflow incontinence associated with BPH • Take with a meal	Y
Tamsulosin (Flomax®)	Initial: 0.4mg PO QD MDD: 0.8mg/day	Capsule: 0.4mg	• Urinary Retention; Urge or Overflow incontinence associated with BPH • Dose titration usually not required • Higher incidence of erectile dysfunction • Lower incidence of syncope, may be a better option for patients with high risk of falls • May open capsule and sprinkle contents into acidic foods such as apple sauce or orange juice	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ALPHA ADRENERGIC RECEPTOR BLOCKERS (CONTINUED)				
Terazosin (Hytrin®)	Initial: 1-2mg PO QD MDD: 20mg/day	Capsule: 1mg, 2mg, 5mg, 10mg	• Urinary retention; urge or overflow incontinence associated with BPH • Helps to relax bladder and allow emptying • Often used for treatment of hypertension	N
URINARY ANALGESICS				
Lidocaine gel (Xylocaine)	Initial: Anesthesia of male urethra: 5-30ml (100 to 600mg); Anesthesia of female urethra: 3-5ml (60 to 100mg) MDD: 1,200mg/day	Topical jelly (Uro-jet): 2%	• Use as comfort measure prior to catheter insertion • No more than 30ml (600mg) should be given in any 12-hour period	-
Phenazopyridine (Pyridium , AZO-gesic)	Initial: 100-200mg PO TID MDD: 600mg/day	Tablet: 95mg, 97.5mg, 100mg, 200mg	• Incontinence associated with dysuria • Consider use if patient experiences dysuria • May cause stomach upset, take with food • Produces an orange to red color in the urine and may stain fabric • Yellowing of the skin or sclera may indicate accumulation due to impaired renal impairment; consider discontinuation • Typically used for shorter periods of time (2-3 days) since can mask signs and symptoms of UTI • Contraindicated if CrCl < 50ml/min	Y

References

- American Urological Association. Chapter 1: Guideline on the management of benign prostatic hyperplasia (BPH). In: Management of benign prostatic hyperplasia (BPH). Revised, 2010. www.auanet.org/common/pdf/education/clinical-guidance/Benign-Prostatic-Hyperplasia.pdf
- Barrisford, G. et al. Acute urinary retention, UpToDate, literature review current through Nov. 2015.
- Bremnor JD, Sadovsky R. Evaluation of Dysuria in Adults. Am Fam Physician 2002;65(8);1589-1596
- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 229, 394.
- Campbell A, Reinken J, McCosh L. Incontinence in the elderly: prevalence and prognosis. Age Aging 1985;14:65–70.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 275-287.
- Cook, K, Sobeski, L. Urinary Incontinence in the Older Adult. PSAP 2013 Special Populations
- Department of Health and Human Services Centers for Medicare & Medicaid Services. Medicare Program:FY 2016 Hospice Wage Index and Payment Rate Update and Hospice. Available online http://federalregister.goca/2015-10422 or FDsvs.gov
- Ferrell, BR and Coyle N (eds). (2001) Textbook of Palliative Nursing. Oxford University Press, Oxford
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 148,159-163.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 690,983-6, 994, 1271.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Lucas MG, Bedretdinova D, Bosch JLHR, et al.; for the European Association of Urology. Guidelines on Urinary Incontinence, 2013.
- Lukacz, E. et al. Treatment of urinary incontinence in women, UpToDate, literature review current through Nov. 2015.
- MacDiarmid, SA. Maximizing the Treatment of Overactive Bladder in the Elderly. Rev Urol. 2008;10(1):6-13
- Mardon RE, Halim S, Pawlson LG, et al. Management of urinary incontinence in Medicare-managed beneficiaries: results from the 2004 Medicare Health Outcomes Survey. Arch Intern Med 2006;166:1128-33.
- McVary, K. et al. Lower urinary tract symptoms in men, UpToDate, literature review current through Nov. 2015.
- Sakakibara R, Ychiyama T, Yamanishi T, et al. Dementia and Lower Urinary Dysfunction: With a reference to anticholinergic use in elderly population. International Journal of Urology (2008):15;778-788
- Sarma A, Wei JF. Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms. N Engl J Med 2012;367:248-57.
- Schappert GT, Bercovitz A, et al. Prevalence of Incontinence among older Americans. National Center for Health Statitics. Vital Health stat 3(36) 2014
- Wells, B. et al. Pharmacotherapy Handbook, 8th ed. 2012, pp. 1058-1066.

OnePoint®
PATIENT CARE

What one can do.®

Pediatric Monographs

Pediatric Constipation

DEFINITION[1]

- Decreased stool frequency from baseline with delay or difficulty in defecation.

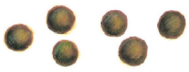
CAUSES

- Medications:
  - » Opioids
  - » Anticholinergic
    - ° Antisecretory drugs
    - ° Tricyclic antidepressants
    - ° Urinary antispasmodics
    - ° 1st generation antihistamines
  - » Diuretics
  - » Antihypertensives
    - ° Alpha-blockers, beta-blockers, calcium channel blockers
  - » Anticonvulsants
    - ° Oxcarbazepine, carbamazepine, phenobarbital, lamotrigine, gabapentin
  - » Vitamins / supplements
    - ° Calcium
    - ° Iron
- Obstruction
  - » Tumor
  - » Stricture
- Neurologic dysfunction
- Symptom of another condition:
  - » Hirschprung disease
  - » Hypothyroidism

HOW TO RECOGNIZE SYMPTOMS

- Clinical characteristics may include:
  - » Hard, dry, or lump stools
    - ° Stool types 1 & 2 on the Bristol Stool Chart (**Figure 1**) are consistent with constipation[2]
  - » Stools that are difficult or painful to pass
  - » Feeling that not all stool has been evacuated
- Decreased stooling frequency from baseline
- Straining, discomfort, pain during bowel movements
- Distended or firm abdomen
- Secondary effects of constipation may include:
  - » Decreased oral intake
  - » Fecal or urinary accidents

FIGURE 1: BRISTOL STOOL CHART[2]

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

CLINICAL INSIGHTS

- Frequency of bowel movements varies based on age and diet. Typical average daily bowel movement (BM) frequencies for non-hospice pediatric patients are as follows[3]:
  - » 0-3 months (formula fed): 2.9 BM/day
  - » 0-3 months (breast fed): 2.0 BM/day
  - » 6-12 months: 1.8 BM/day
  - » 1-3 years: 1.4 BM/day
  - » 3 years and older: 1.0 BM/day
- Prevention of constipation is the most effective management tool. Bowel regimens should be added when patients are receiving opioids and can be considered proactively in patients with known predisposition to constipation.

Pediatric Constipation

- Pediatric patients who experience painful constipation may attempt to withhold or prevent stool due to fear of pain. Withholding may lead to large fecal masses and dilated rectum further potentiating the problem.
- Encopresis, leakage of stool around a large, dry or impacted stool, also known as stool soiling, can occur in toddler age and young children. It is a sign of chronic constipation, not diarrhea or illness.
- Nonpharmacological measures, including adequate fluid intake, increased dietary fiber, probiotics, and scheduled toileting should be employed along with medication therapy.
- Rectal disimpaction of existing dry, hard stools may be necessary for long standing constipation prior to starting a laxative regimen. This can be done manually or in combination with rectally administered agents.
- Excessive dosing of laxatives can cause diarrhea and dehydration.

MEDICATION SPECIFICS:

- Osmotic agents, especially polyethylene glycol, are first line laxatives in the pediatric population due to their benign nature, tolerability, and ability to titrate.
  - » Alternate options: senna and docusate, glycerin, lactulose, magnesium hydroxide
- Patient specific factors and age also influence laxative selection; for example:
  - » Senna with or without docusate should be used first in patients with opioid-induced constipation
  - » Glycerin is first line in infants
- Magnesium or phosphate containing products are not first line agents due to the risk for electrolyte disturbance and should be avoided in patients with kidney dysfunction due to accumulation.
- Suppositories and enemas are generally not recommended if:
  - » Undergoing immunosuppressive or myeloablative chemotherapy due to risk of translocation of GI pathogens to the bloodstream
  - » Significant thrombocytopenia or bleeding diathesis
- Prokinetic agents can be used on their own or in combination with other agents in patients with constipation due to dysmotility.
- Laxatives and prokinetic drugs should be avoided in the context of bowel obstruction, except:
  - » Docusate can be used if partial obstruction
  - » Prokinetic drugs can be used cautiously if partial obstruction, but should be discontinued if colicky pain develops
- Peripherally acting mu-antagonists (methylnaltrexone and naloxegol) are only indicated in adult patients. However, based on information from case reports, off-label use can be considered in pediatric patients with refractory opioid-induced constipation.
- Lubiprostone and linaclotide are both approved for adult use only and are not typically useful in the hospice setting. Small studies have evaluated off-label lubiprostone use in pediatric patients, but linaclotide is not recommended for use in this population. Because of their low utility and lack of evidence supporting use in pediatrics, they are not included in the drug information table.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
STIMULANT LAXATIVES				
Senna (Senokot, Ex-Lax)[4-9]	Initial: 2-5 years old: ½ tablet or teaspoonful (4.3-4.4mg) PO QD ≥6 years old: 1 tablet or teaspoonful (8.6-8.8mg) PO QD MDD: 2-5 years old: 17.2-17.6mg/day 6-11 years old: 34.4-35.2mg/day (≥12 years old): 68.8-70.4mg/day	Syrup: 8.8mg/5ml Tablet: 8.6mg	• Onset of action: 6-24 hours • PRN or scheduled use • Best for short-term / intermittent use • Syrup can be mixed with juice, milk, or ice cream to mask taste	Y
Senna / Docusate (Senna-S)[6,9]	Initial: 2-5 years old: ½ tablet PO daily ≥6 years old: 1 tablet PO daily MDD: 2-5 years old: 2 tablets/day 6-11 years old: 4 tablets/day (≥12 years old): 8 tablets/day	Tablet: 8.6mg sennosides – 50mg docusate	• Combination of stimulant laxative and stool softener • See individual drugs for additional comments	Y
Bisacodyl (Dulcolax)[4-7,9]	Initial (PO): 2-11 years old: 1-2 tablets QD PRN (≥12 years old): 1-3 tablets QD PRN Initial (PR): 2-11 years old: ½ to 1 suppository rectally QD PRN (≥12 years old): 1 suppository or 1 enema rectally QD PRN MDD (PO, PR): 1 dose QD PRN	Enema: 10mg/30 mL Suppository: 10mg Tablet (EC): 5mg	• Onset of action: 6-12 hours (oral); 15-60 min. (suppository); 5-20 min. (enema) • Generally PRN use only • Administer tablet on an empty stomach with water • Retain suppository in rectum for 15-20 min. • Tablet is small enough to be taken by someone who does not regularly swallow pills	N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OSMOTIC LAXATIVES				
Magnesium Citrate (Citroma)[6,8,9]	Initial: 2-5 years old: 60ml PO as a single or divided dose 6-11 years old: 90ml PO as a single or divided dose ≥12 years old: 150ml PO as a single or divided dose MDD: 2-5 years old: 90ml/day 6-11 years old: 150ml/day ≥12 years old: 300ml/day	Oral solution: 1.745gm/30ml, 1.75gm/30ml	• Onset of action: 0.5-6 hours • Generally PRN use only • Use of magnesium citrate has generally been replaced with other laxatives less likely to cause adverse effects (electrolyte disturbances) • To increase palatability, chill the solution before administration • Solution should be taken on empty stomach with 8oz of liquid • Caution, may accumulate in renal impairment	-
Magnesium Hydroxide (Milk of Magnesia) [6,7,9]	Initial: 1-5 years old: 400mg/day PO in single or divided doses 6-11 years old: 1,200mg/day PO in single or divided doses ≥12 years old: 2,400mg/day in single or divided doses MDD: 1-5 years old: 1,200mg/day 6-11 years old: 2,400mg/day ≥12 years old: 4,800mg/day	Chewable tablet: 400mg Oral suspension: 400mg/5ml, 1,200mg/5ml	• Onset of action: 0.5-6 hours • PRN or scheduled use • Preferred magnesium salt for constipation • All doses should be followed by 4-8oz of water • Caution, may accumulate in renal impairment *(Continued on next page)*	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OSMOTIC LAXATIVES (CONTINUED)				
Sodium Phosphate (Fleet Enema, Pedia-Lax Enema)[6,7,9]	Initial: <u>2-5 years old:</u> ½ bottle (~30ml) of children's enema or ¼ bottle (~30ml) of adult enema PR once <u>6-11 years old:</u> 1 bottle (59ml) of children's enema or ½ bottle (~60ml) of adult enema PR once <u>≥12 years old:</u> 1 bottle (118ml) of adult enema PR once MDD (all ages): 1 dose/day	Enema: 3.5gm-9.5gm/59ml (children's), 7gm-19gm/118ml (adult)	• Onset of action: 2-5min • PRN use only • Caution, may accumulate in renal impairment • Avoid frequent use • Not recommended in patients <2 years due to concern for electrolyte imbalances and dehydration	-
Lactulose (Enulose) [5,7,9]	Initial: 1gm/kg (1.5ml/kg) PO in single or divided doses -OR- 5-10ml PO Q2 hours until BM MDD: 2gm/kg/day (3ml/kg/day) or 60ml PO	Packet: 10gm, 20gm Syrup: 10gm/15ml	• Onset of action: variable, 8-48 hours • PRN or scheduled use • May mix with fruit juice, water, or milk	-
Polyethylene Glycol 3350 (Miralax)[5-7,9]	Initial: 0.2-1gm/kg/day PO QD Relative max: 34gm/day	Powder: 17gm per capful / packet	• Onset of action: variable, 1-4 days • Superior to other osmotic agents in palatability and acceptance by pediatrics • Scheduled use is most effective; individualize dosing based on response (ie, may adjust from a few times per week up to BID to produce normal BM frequency) • Stir powder in a ratio of 1 cap (17mg) to 8oz liquid until dissolved • Occasionally, it is necessary to exceed the relative max daily dosing	-
Sorbitol[5,6,9]	Initial: 1-3ml/kg/day PO in single or divided doses MDD: 60ml/day single dose, 90ml/day in divided doses	Oral solution: 70%	• Onset of action: variable, 8-48 hours • PRN or scheduled use • Excessively sweet taste	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
PROKINETIC AGENTS				
Erythromycin (EES, Erypred, Ery-Tab)[6]	Initial: 2.5mg/kg/dose PO BID-QID MDD: 10mg/kg/dose or 250mg/dose, whichever is less; 1,000mg/day	Capsule (DR): 250mg Oral suspension: 200mg/5ml, 400mg/5ml Tablet (stearate): 250mg, 500mg Tablet (EC): 250mg, 333mg, 500mg	• Reserved for metoclopramide intolerant patients • IR tablets, stearate, should be administered on empty stomach due to differences in absorption • Administer 30 min. prior to eating	N
Metoclopramide (Reglan)[6,9]	Initial (PO/IV/PR): 0.1-0.2mg/kg Q6 hours Max: 0.5mg/kg or 10mg per dose, whichever is less; 40mg/day	Orally Disintegrating Tablet (ODT): 5mg, 10mg Oral solution: 5mg/5ml Solution for injection: 5mg/ml Tablet: 5mg, 10mg	• Due to dopamine antagonism, extrapyramidal symptoms (EPS) are common in children; consider administering with diphenhydramine. Note: diphenhydramine can be constipating. • EPS risk increases with dose	Y
STOOL SOFTENER				
Docusate sodium (Colace)[6-9]	Initial (PO): 2-11 years old: 100mg PO daily in single or divided doses ≥12 years old: 200mg PO daily in single or divided doses Initial (PR): 2-11 years old: One 100mg enema PR once ≥12 years old: One 283mg enema PR once Relative MDD (PO): 2-11 years old: 300mg PO daily in single or divided doses ≥12 years old: 500mg PO daily in single or divided doses MDD (PR): 2-11 years old: 1 dose/day ≥12 years old: 3 doses/day	Capsule*: 50mg, 100mg, 250mg Enema: 100mg/5 mL 283mg/5 mL Oral solution: 50mg/5 mL Syrup: 60mg/15 mL Tablet: 100mg	• Onset of action: 12-72 hours • PRN or scheduled use • Liquid products have a bitter taste, may mix with milk, fruit juice, or infant formula to mask taste • Adjust / individualize dosing based on response. Patients may require higher doses than relative maximum. There is no established toxic dose.	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MISCELLANEOUS				
Glycerin (PediaLax)[6,9]	Initial: <5 years old: 0.5-1gm PR QD PRN ≥6 years old: 1-2gm PR QD PRN MDD:1 dose/day	Suppository: 1gm, 1.2gm, 2gm	• Onset of action: 15-30 min. • PRN use only • Retain suppository in rectum for 15 min. or as long as possible • Beneficial for hard, dry stools • Preferred option in infants	-
PERIPHERAL MU ANTAGONISTS				
Methylnaltrexone (Relistor)[10,11]	Initial (SQ): 0.15mg/kg/dose MDD (SQ): 1 dose every 48 hours	Solution for injection: 8mg/0.4ml, 12mg/0.6ml	• Onset of action: 1-4 hours • Occasionally, the 1st dose will not provide laxation and onset may be delayed until subsequent doses are administered • For PRN use in patients with severe, refractory opioid-induced constipation • Use vials, not pre-filled syringes to allow flexibility with pediatric weight-based dosing • An oral formulation exists but use has not been studied in pediatrics	-
Naloxegol (Movantik)[12]	Initial: 0.2-0.6mg/kg MDD: 25mg/day	Tablet: 12.5mg, 25mg	• Onset of action: 6-12 hours • Scheduled use • Administer on an empty stomach at least 1 hour prior to or 2 hours after the first meal of the day • For use in patients with severe, refractory opioid-induced constipation	Y

References

1. National Institute of Diabetes and Digestive and Kidney Diseases (2021). Constipation. Retrieved April 18,2021 from: https://www.niddk.nih.gov/health-information/digestive-diseases/constipation
2. Koppen IJN, Velasco-Benitez C, at al. Using the Bristol Stool Scale and Parental Report of Stool Consistency as Part of the Rome III Criteria for Functional Constipation in Infants and Toddlers. J Ped. 2016;177: P44-48.
3. Evaluation and Treatment of Constipation in Infants and Children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, Journal of Pediatric Gastroenterology and Nutrition. 2006; 43(3): e1-e13
4. Biggs WS, Dery WH. Evaluation and treatment of constipation in infants and children. Am Fam Physician. 2006 Feb 1;73(3):469-77. PMID: 16477894.
5. Evaluation and Treatment of Constipation in Infants and Children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, Journal of Pediatric Gastroenterology and Nutrition. 2006; 43(3): e1-e13
6. Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; December 2020
7. Micromedex Solutions, Ann Arbor, Michigan: Truven Health Analytics; December 2020
8. Santucci G, Mack JW. Common gastrointestinal symptoms in pediatric palliative care: nausea, vomiting, constipation, anorexia, cachexia. Pediatr Clin North Am. 2007 Oct;54(5):673-89, x. doi: 10.1016/j.pcl.2007.06.001. PMID: 17933617.
9. Author Opinion
10. Flerlage JE, Baker JN. Methylnaltrexone for opioid-induced constipation in children and adolescents and young adults with progressive incurable cancer at the end of life. J Palliative Med. 2015; 18(7):631-3.
11. Rodrigues A, Wong C, et al. Methylnaltrexone for opioid-induced constipation in pediatric oncology patients. Pediatr Blood Cancer. 2013;60(1):1667-70.
12. Novak C, Hogg A, et al. Peripherally acting mu-opioid receptor antagonists for treatment of opioid-induced constipation in children. Paediatr Child Health. 2021;26(2):e105-e109.

Pediatric Nausea & Vomiting

DEFINITIONS[1]

- Nausea: An unpleasant, painless sensation to imminently vomit; however, it may or may not result in vomiting.
- Vomiting: Involuntary abdominal contraction and elevation of diaphragm leading to forceful expulsion of gastric contents.

CAUSES

- Five neurotransmitters (histamine, dopamine, serotonin, acetylcholine, and substance P) mediate emetogenic neurotransmission at their respective receptors in two areas of the brain, the vomiting center and chemoreceptor trigger zone. Medications that block these receptors are used to prevent or treat nausea and vomiting.[2-7] (**Figure 1**)
- "AVOMIT" is a useful acronym for common causes of nausea and vomiting, including anticipatory, vestibular, obstructive, dysmotility, infection / inflammation, and toxins (inc. medications)[2] (**Table 1**).

FIGURE 1: NAUSEA AND VOMITING RECEPTOR PROFILES, MECHANISMS, AND PATHOPHYSIOLOGY

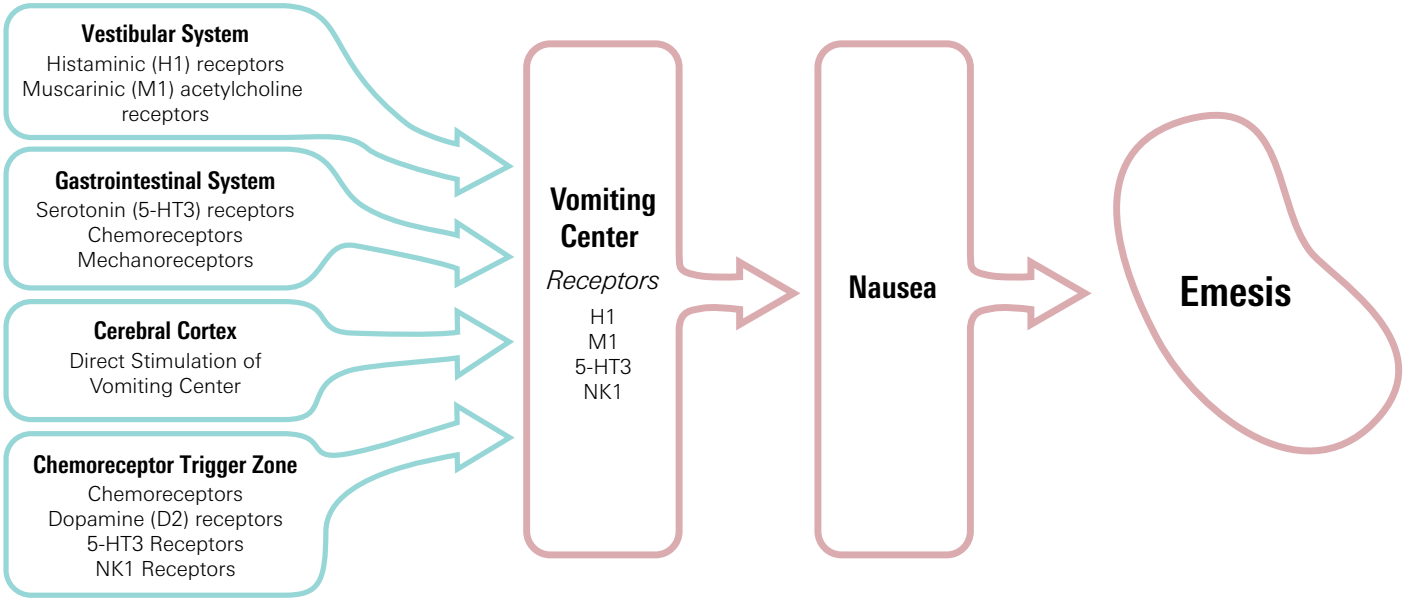


TABLE 1: SOURCES OF NAUSEA AND VOMITING WITH CORRESPONDING TREATMENT OPTION USING ACRONYM "AVOMIT"

	Cause	Example	Receptor / Pathway	Treatment agent(s)
A	Anticipatory / Anxiety	Psychogenic vomiting, anxiety, depression	Stimulation of chemoreceptor trigger zone and vomiting center	Benzodiazepine
V	Vestibular	Labyrinthitis, tumors, Meniere's disease	Acetylcholine, histamine	Anticholinergic, Antihistamine
O	Obstructive	Constipation, gastric outlet, small bowel obstruction	Afferent nervous system	Olanzapine, antispasmodics, prokinetics, other
M	dys**M**otility	Neuromuscular disorder: Gastroparesis, chronic intestinal pseudo-obstruction	Afferent nervous system, acetylcholine, histamine, serotonin	Prokinetics
I	Infection / Inflammation	Gastroenteritis, peptic ulcer disease, cholecystitis, pancreatitis, Crohn's disease	Histamine, acetylcholine	Anticholinergic, Antihistamine
T	Toxin / Medication	• Chemotherapy, antibiotics / antivirals, anticonvulsants, opioids • Endocrine and metabolic disorders: Uremia, parathyroid disease, hyperthyroidism	Serotonin, dopamine, Neurokinin	Serotonin antagonists, dopamine antagonists, NK1 antagonist

- Additional triggers of nausea:
  - » Functional disorders: functional dyspepsia, chronic idiopathic nausea, idiopathic vomiting, cyclic vomiting syndrome, irritable bowel syndrome
  - » Central nervous system conditions: migraine, increased intracranial pressure, hydrocephalus
  - » Miscellaneous: cardiac disease (including cardiomyopathy), radiation therapy

HOW TO RECOGNIZE SYMPTOMS

- The Baxter Retching Faces (BARF) scale is a validated, pictorial nausea rating scale for use in children.[8]
- Nausea and vomiting are frequently accompanied by sweating, pallor, hypotension, and dizziness.
- Prolonged nausea and vomiting may be indicative of an obstruction, metabolic disorder or cyclic vomiting syndrome.
- Gastroenteritis is associated with sudden, painless onset and is often accompanied by fever and diarrhea.[9]
- Peptic ulcer disease generally presents with epigastric pain, blood/coffee ground-like substance in vomit. Vomiting usually occurs during or after meals. Symptoms, including pain, typically resolve with acid blockade.[9]
- Gastro-esophageal reflux disease (GERD) is characterized by effortless regurgitation (no retching) and usually accompanied by fussiness, irritability and feeding aversion in pediatrics. Back arching is a common presentation of GERD in infants.
- Early morning nausea & vomiting may be indicative of increased intracranial pressure or cyclic vomiting syndrome.
- Feculent or bilious vomit may indicate a small bowel obstruction.

CLINICAL INSIGHTS

- Younger patients, especially those with developmental delay or intellectual disability, are frequently not able to describe the feeling of nausea.[1]
- When possible, the choice of medication should be based on presumptive triggers / causes and associated neurotransmitters / receptors (**Table 1**).
  - » Serotonin (5-HT_3) receptor blockers like ondansetron are commonly used for viral gastroenteritis and are helpful in chemotherapy-induced nausea and vomiting. They are a reasonable initial agent for an unknown etiology.[9]
  - » Acid suppressants are useful for GERD-induced nausea.
  - » For nausea and vomiting due to constipation-induced obstruction, address the underlying problem (see constipation monograph), then follow with symptomatic treatment.
  - » Dexamethasone is useful in patients with chemotherapy-induced nausea and vomiting, increased intracranial pressure, and tumor burden.[9]
  - » Anticholinergic agents:
    - ° Dose conservatively to avoid excessive drying and resultant thick secretions that can lead to mucus plugging and worsening symptoms.
    - ° When excess secretions are a source of nausea/vomiting, glycopyrrolate and hyoscyamine can improve symptoms.
    - ° Agents with antispasmodic properties, such as dicyclomine and hyoscyamine, can alleviate intestinal spasms which lead to nausea or GI intolerance.
  - » Anticipatory or anxiety-induced nausea and vomiting remain a potential trigger even after discontinuing aggressive interventions such as chemotherapy. Anti-anxiety medications such as hydroxyzine and benzodiazepines can be trialed.

- A number of medications act on multiple receptors and therefore can target different etiologies:
  - » Olanzapine: serotonin antagonist, dopamine antagonist, antihistamine, alpha antagonist
  - » Metoclopramide: dopamine antagonist, serotonin antagonist, enhances response to acetylcholine in upper GI tract
- Use extreme caution when administering dopamine antagonists to pediatric patients. The 'KIDs List,' or Key Potentially Inappropriate Drugs in Pediatrics, recommends avoiding this class in infants and using caution in older children. They classify this as a strong recommendation due to risk of acute dystonia, respiratory depression, extravasation, and death with intravenous use.[10]
  - » If use is warranted, diphenhydramine can be administered 30 minutes prior to decrease risk of extrapyramidal symptoms (EPS).
- Patients undergoing emetogenic chemotherapy should receive preemptive and scheduled antiemetics based on the degree of emetogenicity or as recommended by treatment protocol.
  - » Children's Oncology Group has endorsed standard protocols and developed a supportive care guideline outlining recommendations.[11]
- The best treatment for motion sickness is to avoid the trigger, but anticholinergics and antihistamines may be used as prophylaxis and/or treatment.[9]
- Gastroenteritis is often treated with oral rehydration therapy and rarely requires pharmacotherapy.[12]
- Non-pharmacologic therapy:
  - » Avoid triggers such as certain foods, beverages, and motions.
  - » Modify feeding regimen to include smaller, more frequent meals.
  - » Numerous behavioral interventions can be used to retrain and reorient the brain and serve as adjuncts to traditional medications. Examples include relaxation, progressive muscle relaxation, biofeedback, hypnosis, yoga, acupuncture, accupressure (eg, use of SeaBands®), cognitive distraction, systemic desensitization, and herbals and supplements (eg, ginger, peppermint / chamomile teas).

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
1ST GENERATION ANTIPSYCHOTICS / TYPICAL				
Prochlorperazine (Compazine)[13-14]	Initial (PO/PR/IM): ≥2 years old 0.1-0.15mg/kg Q8-12 hours Max: 10mg/dose; 40mg/day	Solution for injection: 5mg/ml Suppository: 25mg Tablet: 5mg, 10mg	**1st Generation Antipsychotics** • Reserve for patients who are not responsive to other antiemetics because pediatric patients are at increased risk of adverse effects including dystonia • Use with caution in patients at risk for seizure; dopamine antagonists can lower seizure threshold **Prochlorperazine** • Do not give SQ; may cause tissue damage • IV route is not preferred due to higher risk of dystonia and akathisia **Haloperidol** • May cause QT prolongation	Y
Haloperidol (Haldol)[14-15]	Initial (PO): ≥3 years old 0.01-0.02mg/kg Q8-12 hours Max: 1mg/dose; 2mg/day	Oral solution: 2mg/ml Tablet: 0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg		Y
2ND GENERATION / ATYPICAL ANTIPSYCHOTICS				
Olanzapine (Zyprexa)[14]	Initial (PO): 0.1-0.14mg/kg Q12-24 hours MDD: 20mg/day	Orally Disintegrating Tablet (ODT): 5mg, 10mg, 15mg, 20mg Tablet: 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg	• Dose must be rounded to closest 1.25mg increment • Risk of hyperprolactinemia is greater in adolescents than in adults • Limited data in patients 4-12 years old; use with caution	Y
5-HT$_3$ RECEPTOR ANTAGONIST				
Ondansetron (Zofran)[14]	Initial: 0.15mg/kg PO/IV Q8 hours Max: 8mg/dose; 24mg/day	Orally Disintegrating Tablet (ODT): 4mg, 8mg Oral solution: 4mg/5ml Solution for injection: 2mg/ml Tablet: 4mg, 8mg	• Use with caution in patients with congenital long QT syndrome or other risk factors for QT prolongation	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICHOLINERGIC AGENTS				
Dicyclomine (Bentyl)[14]	Initial (PO): <u>>6 months old:</u> 5mg Q6-8 hours <u>>2 years old:</u> 10mg Q6-8 hours <u>>12 years old:</u> 10-20mg Q6-8 hours Max: same as initial dosing	Capsule: 10mg Oral solution: 10mg/5ml Tablet: 20mg	• Contraindicated in infants <6 months old due to increased adverse effects such as seizures, respiratory distress, and syncope • Diluting the oral solution 1:1 with water can improve bitter flavor • For motility disorders, administer 30 minutes prior to eating	Y
Glycopyrrolate (Robinul)[14]	Initial (PO): 20-40mcg/kg Q4-8 hours Initial (IM/IV): 4-5mcg/kg Q3-4 hours Max (PO): 100mcg/kg/dose or 2mg/dose, whichever is less; 300mcg/kg/day or 8mg/day Max (IV): 10mcg/kg/dose or 0.2mg/dose, whichever is less; max 6 doses per day	Oral solution: 1mg/5ml Solution for injection: 0.2mg/ml Tablet: 1mg, 1.5mg, 2mg	• Exercise caution when dosing, double-checking units • For best absorption, solution should be given on an empty stomach 1 hour before or 2 hours after meals	Y
Hyoscyamine (Levsin, Hyomax-SL)[14]	<u><2 years old:</u> <u>3.4-5kg:</u> 4 drops (0.01375mg) PO/SL Q4 hours PRN <u>5-7kg:</u> 5 drops (0.0175mg) PO/SL Q4 hours PRN <u>7-10kg:</u> 6 drops (0.02mg)PO/SL Q4 hours PRN <u>≥10kg:</u> 8 drops (0.0275mg) PO/SL Q4 hours PRN <u>2-12 years old:</u> 0.0625-0.125mg PO/SL Q4 hours PRN MDD: same as initial dosing	Oral solution: 0.125mg/ml Orally Disintegrating Tablet (ODT): 0.125mg Tablet: 0.125mg	• Use the dropper that comes with the package, which is marked with specific graduations; 3, 4, or 5 drops or 0.25ml • For the 0.125mg/ml solution, 1ml contains about 36 drops of solution when using the dropper from the package	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Scopolamine (Transderm Scop)[14]	Initial: <u><2 years old:</u> ¼ patch topically Q3 days <u>2-6 years:</u> ½ patch topically Q3 days <u>6-12 years:</u> ½-1 patch topically Q3 days <u>12+ years:</u> 1 patch topically Q3 days Max: 1 patch Q3 days	Transdermal patch: 1.5mg (1mg/3 days)	• Takes about 12 hours to reach peak effect • Patch should not be cut • May apply transparent film dressing (eg, Tegaderm) below patch in order to administer a partial dose or only remove part of the backing	-
ANTIHISTAMINES				
Dimenhydrinate (Dramamine)[13-14,16]	Initial: <u>2 to 12 years old:</u> 1-1.5mg/kg Q6 hours (Max dose: 50mg) <u>>12 years old:</u> 50-100mg Q4-6 hours PRN MDD (PO): <u><6 years old:</u> 75mg/day <u>6 to 12 years old:</u> 150mg/day <u>13 to 18 years old:</u> 400mg/day	Chewable tablet: 50mg Tablet: 50mg	**Antihistamines** • Usually cause sedation, but can cause paradoxical hyperexcitability in pediatric patients **Dimenhydrinate** • Composed of approximate 1:1 ratio of diphenhydramine and 8-chlorotheophylline, a mild stimulant with effects similar to caffeine. The latter is included with the intent to offset the sedative effect of diphenhydramine, although the clinical significance of this is questionable. • 50mg dimenhydrinate provides approximately 25mg diphenhydramine	Y
Diphenhydramine (Benadryl)[13]	Initial (PO/IV): <u>≥2 years old:</u> 0.5mg-1.25mg/kg Q6 hours Max: 50mg/dose; 200mg/day	Capsule: 25mg, 50mg Chewable tablet: 12.5mg Oral solution: 12.5mg/5ml Solution for injection: 50mg/ml Tablet: 25mg, 50mg		Y
Meclizine (Antivert)[14]	Initial: <u>≥2 years old:</u> 12.5-25mg PO Q8 hours MDD: 100mg/day	Chewable tablet: 25mg Tablet: 12.5mg, 25mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
PROKINETIC AGENTS				
Metoclopramide (Reglan)[14]	Initial (PO/IV/PR): 0.1-0.2mg/kg Q6 hours Max: 0.5mg/kg or 10mg per dose, whichever is less; 40mg/day	Oral solution: 5mg/5ml Orally Disintegrating Tablet (ODT): 5mg, 10mg Solution for injection: 5mg/ml Tablet: 5mg, 10mg	• Due to dopamine antagonism, extrapyramidal symptoms (EPS) are common in children; consider administering with diphenhydramine • EPS risk increases with dose	Y
Erythromycin (EES, Erypred)[14]	Initial: 2.5mg/kg PO Q6 hours Max: 10mg/kg/dose or 250mg/dose, whichever is less; 1,000mg/day	Capsule (DR): 250mg Oral suspension: 200mg/5ml, 400mg/5ml Tablet (stearate): 250mg, 500mg Tablet (EC): 250mg, 333mg, 500mg	• Reserved for metoclopramide intolerant patients • IR tablets, stearate, should be administered on empty stomach due to differences in absorption • Administer 30 minutes prior to eating	N
CORTICOSTEROID				
Dexamethasone (Decadron)[11,14]	Initial (PO/IM/IV): 0.15mg/kg/dose Q6 hours OR as recommended by oncology protocol Max: 0.3mg/kg/dose; 20mg/day	Oral solution: 0.5mg/5ml, 1mg/ml Solution for injection: 2mg/ml, 4mg/ml Tablet: 0.5mg, 0.75mg, 1mg, 1.5mg, 2mg, 4mg, 6mg	• Give with food/milk to reduce GI upset • If using >2 weeks, withdraw slowly due to concerns for adrenal suppression • Decrease dose by 50% if in combination with aprepitant	Y
ACID SUPPRESSANTS				
Famotidine (Pepcid) [14,16]	Initial (PO): 0.5mg/kg Q12-24 hours Max: 40mg/dose; 2mg/kg/day or 80mg/day, whichever is less.	Oral suspension: 40mg/5ml Tablet: 20mg, 40mg	H2-Receptor antagonists • May be taken without regard to meals • Can be taken regularly or on as needed basis for symptoms	Y
Omeprazole (Prilosec) [14,16]	Initial: 1mg/kg QD MDD: 4mg/kg/day or 40mg/day, whichever is less	Capsule (DR): 10mg, 20mg, 40mg Orally Disintegrating Tablet (ODT): 20mg Packet: 2.5mg, 10mg Suspension: 2mg/ml Tablet (DR/EC)*: 20mg	• Best if taken 30 minutes prior to a meal • May divide doses twice daily if wearing off effect • Packet / suspension are expensive	N*/Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER				
Cyproheptadine [1,14,17] (Periactin)	Initial (PO): 0.125-0.25mg/kg/dose Q8-12 hours MDD: 16mg/day	Oral solution: 2mg/5ml Tablet: 4mg	• Potent antihistamine with additional serotonin antagonism and anticholinergic effects • May be useful for patients who have retching or feeding intolerances[3] • Usually given 2-4 times daily, but can give once at bedtime if excessive daytime sedation[3]	Y
Aprepitant (Cinvanti, Emend)[14,17]	Initial (PO): ≥6 months & <30kg: 3mg/kg day 1, 8mg/kg on days 2 & 3 >30kg: 125mg on day 1, 80mg on days 2 & 3 MDD: same as initial	Capsule: 40mg, 80mg, 125mg Oral suspension: 125mg/5ml	• 2nd line option for prophylactic treatment of cyclic vomiting syndrome • Caution with CYP3A4 inhibitors and inducers	Y
Dronabinol (Marinol, Syndros)[14]	Initial: ≥6 years old: 2.5mg PO TID-QID Max: 10mg/dose; 40mg/day	Capsule: 2.5mg, 5mg, 10mg Oral solution: 5mg/ml	• Bioavailability not equivalent between formulations • Generally reserved for patients ≥6 years old; use with caution age 6-12 years old	N

References

1. Di Lorenzo, Carlo MD. Approach to the Infant or Child with Nausea and Vomiting. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com (literature review current through 12/2019)
2. Singh P, Yoon SS, Kuo B. Nausea: a review of pathophysiology of therapeutics. Therap Adv Gastroenterol. 2016; 9 (1): 98-112.
3. Denholm L, Gallagher G. Physiology and pharmacology of nausea and vomiting, Anaesthesia & Intensive Care Medicine. 2018; 19 (9): 513-516.
4. Flake ZA, Scalley RD, Bailey AG. Practical Selection of Antiemetics. Am Fam Physician. 2004;69(5): 1169-1174.
5. Tradounsky G. Palliation of gastrointestinal obstruction. Can Fam Physician. 2012; 58 (6): 648-652.
6. Hallenbeck J. The Causes of Nausea and Vomiting (V.O.M.I.T.) 2nd edition. End of Life/Palliative Education Resource Center (EPERC). 2013. Available from: https://www.med-surg.org/wordpress/wp-content/uploads/palliative-course-handout.pdf
7. Common Gastrointestinal Symptoms in Pediatric Palliative Care: Nausea, Vomiting, Constipation, Anorexia, Cachexia. Pediatr Clin N Am. 2007; 54(5): 673-689.
8. Baxter AL, Watcha MG, Baxter WV, et al. Development and Validation of a Pictorial Nausea Rating Scale for Children. Pediatrics 2011; 127:e1542-1549.
9. Marcdante, Karen, and Robert M. Kliegman. Essentials of Pediatrics, Elsevier, 2018. ProQuest Ebook Central, https://ebookcentral.proquest.com/lib/midwestern/detail.action?docID=5434810.
10. Meyers RS, Thackray J, Matson KL, et al. Key Potential Inappropriate Drugs in Pediatrics: The KIDs List. J Pediatr Pharmacol Ther. 2020; 25 (3): 175-191.
11. Children's Oncology Group. "Guidelines on Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients" COG Supportive Care Endorsed Guidelines. July 2020. Available from: https://childrensoncologygroup.org/downloads/COG_SC_CINV_Guidelines_Document.pdf
12. DiPiro JT. Pharmacotherapy— a Pathophysiologic Approach. New York: McGraw-Hill Education; 2017.
13. Shega JW, Paniagua MA. Pediatric Palliative Care and Hospice: Essential Practices in Hospice and Palliative Medicine. Chicago, IL: AAHPM; 2017
14. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019
15. Siden HB. Haloperidol as a Palliatitve Anti-Emetic in a Toddler: An Evidence Base Challenge. Letter to the Editor. J Pain Symptom Management. 2008; 35(3):235-38.
16. Micromedex: DRUGDEX. Greenwood Village (CO): IBM Corporation; 2020. Available from: www.micromedexsolutions.com.
17. Li, B UK MD. Cyclic Vomiting Syndrome. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. Literature review current through 12/2019)

Pediatric Pain

DEFINITION

Pain is an unpleasant physical and emotional experience due to actual or potential tissue damage. It is subjective and highly individualized. Refer to the adult pain monographs for more information about different types of pain.

Pediatrics refers to anyone under the age of eighteen and is further broken down into one of four categories (**Table 1**).

TABLE 1 - PEDIATRIC AGE

NEONATE	INFANT	CHILD	ADOLESCENT
< 28 days	29 days to 12 months	1 to 9 years	10 to 18 years

COMMON CAUSES FOR PEDIATRIC PAIN

- Trauma / tissue damage / injury
- Cancer and related treatments
- Congenital malformations
- Sickle Cell disease
- Disease progression

TYPES OF PAIN

- Nociceptive pain arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.[1]
  - » Somatic pain is caused by injury or inflammation involving skin, soft tissue, or bone. It is generally well localized and often described as "dull" and "aching."[2]
  - » Visceral pain may be caused by organ distension, such as in the bowels. It is generally poorly localized and may refer or radiate to distant sites.[2]
- Neuropathic pain is caused by a lesion or disease affecting the somatosensory system.[1]

HOW TO RECOGNIZE SYMPTOMS

- Pediatric pain assessment should consider age, developmental stage, pain type, etiology, and presence of neurological impairment.
  - » Pain in pediatric patients often goes unrecognized or is misinterpreted.
  - » Unique behaviors are often displayed, so careful input from family members and caregivers is needed.
  - » Incorrect assessment can lead to unnecessary suffering and long-term consequences.
- The "QUEST" acronym can be used to assess pain in pediatric patients.
  - » **Q**uestion the child / caregiver
  - » **U**se rating tools
  - » **E**valuate behavior (including subtle changes)
  - » **S**ensitize parents / staff
  - » **T**ake action
- Recognizing non-verbal signs of pain is particularly important in pediatric pain management, including:
  - » Agitation or changes in behavior
  - » Changes in body movement or posture
  - » Social withdrawal (children with persistent pain may become quiet, antisocial, and sleep more)
  - » Changes in eating / sleeping patterns
  - » Certain facial expressions commonly associated with pain in infants:
    - ° Facial grimacing
    - ° Brow lowering
    - ° Squeezing eyes shut
    - ° Deepening of "laugh lines"
    - ° Opening lips / mouth
    - ° Cupping tongue
- Children may offer important audible clues.
  - » In younger children, differentiating varying types / sounds of cries can be helpful.
  - » Older children may exhibit groaning, moaning or sighing.
- Children have different abilities to process and express feelings of pain compared to adults.[3]
  - » <2 years: Children know to avoid painful situations and can show signs of anger and sadness if pain is experienced. At approximately 18 months, children can start to indicate where they are feeling pain.
  - » <6 years: Child is unable to anticipate pain relief, even when told, or distinguish causes and consequences of pain.
  - » 6+ years: Child can describe pain as a physical experience localized in their body and relate the cause of pain to the effect of pain.

- 12+ years: Child can understand that pain is due to physical and psychological causes and can be taught coping strategies.

- Although they can be unreliable in critically ill patients, physiological changes can be considered, including increases in heart rate, respiratory rate and blood pressure.
- A number of validated pain scales exist for pain assessment in pediatric patients and they should be employed whenever possible.
  - Neonates / infants
    - CRIES
    - Face, Leg, Activity, Cry and Consolability Score (FLACC)
  - Young children
    - Faces Pain Scale-Revised (FPS-R)
    - OUCHER
    - Wong-Baker Faces
  - Children with cognitive impairment[4]
    - Revised Face, Leg, Activity, Cry and Consolability Score (R-FLACC)
    - Individualized Numerical Rating Scale (INRS)
    - Pediatric Pain Profile (PPP)
    - Non-Communicating Children Pain Checklist – Revised (NCCPC-R)

CLINICAL INSIGHTS

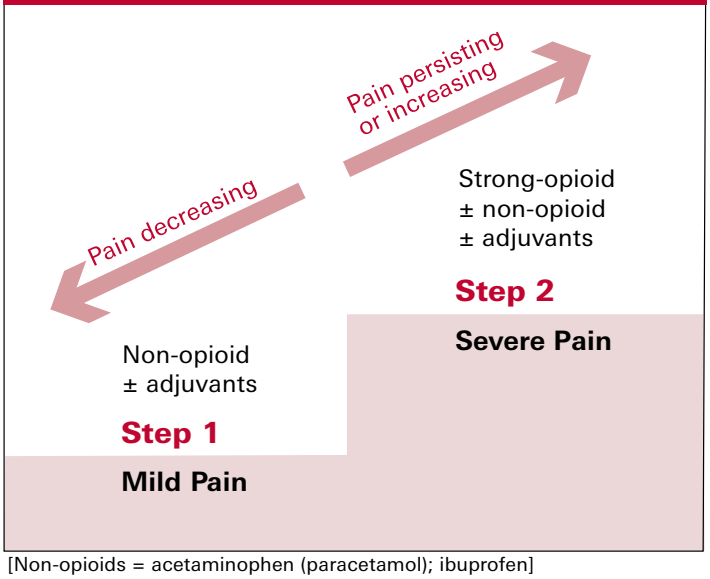
- Some principles of chronic pain management are similar in both pediatric and adult patients:
  - Establish treatment goals
    - Treatment plans should be the simplest ones that will achieve the intended response.
    - Use effective adjuvants and non-pharmacologic treatments.
  - Establishing a scheduled analgesic regimen is a key step to preventing pain
    - Titration of scheduled analgesic regimens should be considered when patients require more than 3 to 4 analgesic doses for breakthrough pain within a 24-hour period.[1]
    - For patients receiving a scheduled opioid regimen, breakthrough opioid doses should be calculated as 10-15% of total daily scheduled doses.[2]
    - Following titration, allow at least 48 hours to assess effectiveness and tolerability prior to attempting subsequent titrations.[3]
  - Evaluate risks for misuse
- Despite the aforementioned similarities, key differences in pediatric pharmacokinetics and pharmacodynamics call for extra caution when selecting and dosing medications.
  - When available, the enteral route (including oral and feeding tube) is preferred.
  - Intramuscular injections should be avoided due to:
    - Fluctuating absorption attributed to reduced muscle mass in pediatric patients
    - Injections are often painful and can cause apprehension to future treatments.
  - Weight-based dosing is preferred in children <16 years of age or <40kg.
    - If the calculated weight-based dose exceeds the recommended adult dose, the adult dose should be used.
  - Topically applied medications generally have increased absorption for several reasons including decreased skin thickness, increased skin hydration, and increased body surface area to weight ratio.
    - Pediatric patients may require more frequent patch changes due to faster drug clearance[5]
- Non-pharmacologic interventions are often useful and should be considered along with drug therapy when possible.
  - Music and art can be used as an outlet for emotions and can decrease anxiety / fear.[3]
  - Massage can relax muscles and ease spasms / aches.[3]
  - Physical comfort measures include the use of hot or cold compresses, application of pressure or vibration, and repositioning.[6]
  - Distraction and guided meditation techniques involve diverting the patient's focus to something such as an activity, imagery, or music during moments of pain.
    - Taste has been utilized as a distraction in infants undergoing minor procedures, using 1.5-2ml of sucrose given by mouth over two minutes.[2]

- Hypnosis to induce physiological, perceptual, sensory and memory changes[3]
- Imagery / imagination / pretending to help to decrease anxiety or alter pain sensations / perceptions[3]

WHO 2-STEP ANALGESIC LADDER FOR PEDIATRIC PATIENTS

- According to the World Health Organization, a 2-step approach (**Figure 1**) is safer and more effective at managing persistent pain in children with medical illnesses than the 3-step approach they recommend for adults.
  - The 2-step version eliminates the second step from the 3-step version that advises using weak opioids such as codeine or tramadol and combination opioids, such as hydrocodone or oxycodone with acetaminophen.
  - The risks of using lower doses of strong opioids are considered acceptable compared to the uncertainty associated with the response to codeine and tramadol in children.[7]

FIGURE 1 – WHO 2-STEP ANALGESIC LADDER



[Non-opioids = acetaminophen (paracetamol); ibuprofen]

- WHO Step 1: Non-opioids (eg, acetaminophen, ibuprofen) are first-line therapies for mild pain in infants and children ≥3 months old, along with appropriate use of adjuvant therapies.
  - Acetaminophen
    - For neonates and infants <3 months old, acetaminophen is the only analgesic recommended for use in step 1.
  - NSAIDs
    - Although general guidelines do not advise use in neonates or infants <6 months, studies have shown that ibuprofen can be used in infants >3 months old if they weigh >5kg and maintain adequate hydration.[8]
    - In neonates and infants <3 months old, NSAIDs are not advised because renal function remains immature and use could cause renal vasoconstriction and decreased renal function via NSAID blockade of prostaglandin production.[8]
    - Ibuprofen has better safety and efficacy data compared to other NSAIDs.
  - Combined use of an NSAID and acetaminophen may have a synergistic effect on pain[9]
    - Simultaneous administration of acetaminophen and ibuprofen/NSAIDs may increase the risk of acute kidney injury.
      - Alternating / staggering doses may decrease this theoretical risk; however, these regimens should be used cautiously as they are more complex and increase risk for dosing / administration errors.
- Codeine and tramadol are contraindicated for the treatment of pain in patients <12 years and have been omitted from the WHO 2-step ladder for pediatrics.[10]
  - Codeine is a prodrug requiring metabolism by CYP2D6 to morphine for analgesia and is not recommended in pediatric patients due to variable metabolism, which can result in fatal overexposure or lack of efficacy.
  - Tramadol is contraindicated for treatment of pain in children <18 years of age after certain surgical procedures and in patients with particular health conditions. Due to safety concerns, tramadol has also fallen out of favor as an analgesic treatment option in all pediatric patients.[10]

- WHO Step 2: Opioids for moderate-to-severe pain
  - » Immediate release morphine is the opioid of choice in pediatric patients.[3]
  - » Initial doses of opioids for neonates and infants <6 months of age are 25-50% lower than older children due to metabolic differences. This dosing difference has already been accounted for in the Drug Information Table below. Morphine is the opioid of choice in this age range due to amount of supporting data relative to other agents.[3]
  - » After typical daily use of short-acting opioids has been established (usually 2 to 3 days), conversion to a long-acting opioid can be considered to reduce administration burden.[3]
- Opioid adverse effects
  - » Efforts to prevent side effects before they occur are particularly important in children because they are more likely to refuse a medication if it causes distressing side effects, even if they are getting adequate pain relief.
    - ° Bowel care regimens should be initiated in children taking opioids to prevent opioid-induced constipation.
  - » Additional opioid side effects include itching, sedation, respiratory depression (additive with other CNS depressing drugs), urinary retention, and neurotoxicity.[11]
    - ° Infants <3 months are more susceptible to opioid-induced respiratory depression due to differences in liver and kidney function, higher body water-to-fat ratio, reduced albumin / glycoproteins, and a reduced respiratory response to changes in O_2 or CO_2.[2]
  - » Opioid-induced neurotoxicity (OIN) can potentially occur with any opioid, but is thought to be more common in opioids with active metabolites, esp. morphine and hydromorphone.[1,12]
    - ° Symptoms include myoclonus, hyperalgesia, allodynia, hallucination, and seizure.
    - ° Risk factors include high dose, longer treatment duration, renal impairment, rapid titration, dehydration, and concomitant use of psychoactive medications.
    - ° Treatment requires opioid rotation plus symptomatic treatment.
  - » When adverse effects, dosage form limitations, or other reasons warrant opioid rotation, consider a 25-50% reduction in the calculated dose of the new opioid to account for incomplete cross-tolerance.[3]
- Methadone should be used with caution and reserved for when other opioids have failed, are intolerable, or when a compelling reason for use exists (eg, neuropathic pain).
  - » Methadone is an NMDA receptor antagonist and norepinephrine reuptake inhibitor – mechanisms that make it more effective for neuropathic pain.[1]
  - » Although methadone is not formulated as an extended release dosage form, its long half-life allows it to be used for long-acting pain relief.
  - » Methadone is a synthetic opioid with a structure distinct from natural opioids, making it a good alternative for patients with true opioid allergies or dose-limiting side effects.[3]
  - » Methadone should only be initiated by an experienced prescriber and the patient should be monitored closely for at least the first week of therapy and following any dose adjustments.
    - ° If excessive sedation occurs, hold dose(s) and consider dose reduction or increasing the dosing interval.
  - » Despite its long half-life, methadone still requires a tapered discontinuation to prevent withdrawal symptoms.

ADJUVANT PAIN MANAGEMENT

- An adjuvant analgesic is a drug that is used as an analgesic in certain circumstances that also has a major clinical use unrelated to pain management.
- Adjuvant therapies increase analgesic efficacy by treating specific types of pain, and should be used simultaneously with opioids when appropriate.
- Neuropathic pain in children can occur in patients with cancer, neurodegenerative diseases or severe neurological impairment (SNI), but is otherwise considered uncommon.

- » It is caused by injury or degeneration of peripheral nerves or the pain pathway in the central nervous system
- » Hallmark features of neuropathic pain include:
  - ° Pain descriptors: burning, shooting, stabbing
  - ° Sensory deficit or disturbance: paresthesia, focal sensory deficit, hypersensitivity, allodynia
  - ° Motor findings: spasms, dystonia, tremor, fasciculation, weakness
  - ° Autonomic disturbances: cyanosis, erythema, mottling, increased sweating, swelling
- » Neuropathic pain should be suspected when pain is not relieved despite treatment and there is no identifiable source of nociceptive pain.
- » Conventional analgesic medications are often partially or completely ineffective in alleviating neuropathic pain.[13]
- » Gabapentinoids (eg, gabapentin, pregabalin) are first-line medications.
- » Tricyclic antidepressants (TCAs) (eg, amitriptyline, nortriptyline), clonidine, and methadone are second-line treatments.

- Children with SNI often have more severe and more frequent episodes of pain than what is typically seen in developing children and are often described as having neuro-irritability / agitation.
  - » Neuro-irritability is defined as unpleasant psychological and physical arousal without an underlying cause.[14]
  - » Dysautonomia, neurostorming, and paroxysmal autonomic instability with dystonia are a collection of syndromes along the same spectrum that may occur in patients with severe brain injury. Symptoms include agitation, diaphoresis, hyperthermia, hypertension, tachycardia, tachypnea, hypertonia, and extensor posturing.[15]
  - » Studies suggest that patients with SNI may benefit from medications that improve central neuropathic pain, decrease sympathetic outflow, and promote muscle relaxation.[7] Such medications include nonselective ß-blockers, α-2 agonists, and benzodiazepines.[15] Notably, these medications lack analgesic properties.
    - ° The α-2 agonist clonidine is especially beneficial with neuro-irritability because it decreases sympathetic output and increases firing of pain-inhibiting neurons.[3]
- Visceral pain in children may be caused by tumors or obstruction.
  - » Corticosteroids may be considered first-line for inflammation, capsular stretching or pleuritic chest pain.
  - » Anticholinergics may be used, but can cause constipation. Fluid consumption and fiber intake should be encouraged.
- Bone pain may be caused by primary bone cancer or osteosarcoma and may need multiple agents to achieve relief.[1]
  - » NSAIDs are first-line for treatment of bone pain.[1]
  - » Corticosteroids can be used as an alternative if NSAIDs are contraindicated or additional therapy is needed.[3]
- Other adjuvants include topical agents, serotonin-norepinephrine reuptake inhibitors, anti-epileptics, and cannabinoids.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)				
Aspirin (Bayer, Ecotrin)[11,16]	Initial: <u><50kg:</u> 10-15mg/kg PO/PR Q4-6 hours <u>≥12 years old & > 50kg:</u> 325mg-650mg PO/PR Q4-6 hours MDD: 90mg/kg or 4,000mg/day	Capsule (EC)*: 325mg Capsule (sodium): 81mg, 325mg, 500mg Tablet: 81mg, 220mg (sodium), 325mg, 650mg Tablet (chewable): 81mg Tablet (EC)*: 81mg, 325mg, 500mg Suppository: 300mg, 600mg	**NSAIDs** • May cause GI upset; take with food or milk[11,16] • Caution in renal and hepatic impairment[11] • Use with caution in patients who have platelet / bleeding disorders as NSAIDs have antiplatelet effects[11,16] **Aspirin** • Not a preferred agent in pediatrics • Not recommended in children recovering from viral infections due to the risk of Reye's syndrome[11,16] • Suppository should be inserted into rectum as far as possible[11]	Y/N*
Celecoxib (Celebrex)[11,16-18]	Initial: <u>≥2 years old:</u> 1-2mg/kg PO Q12-24 hours MDD: 400mg/day	Capsule: 50mg, 100mg, 200mg, 400mg Extemporaneously compounded suspension (10mg/ml): triturate contents of twenty 100mg capsules (or equivalent of another strength) and add to 200ml of Ora-Blend[19]	**Celecoxib** • Extemporaneously compounded suspension allows dosing flexibility and is stable for up to 90 days when stored in an amber bottle with refrigeration or at room temperature[19] • Use with caution in known poor CYP2C9 metabolizers or drugs that inhibit CYP2C9[11,16] • Capsules may be opened and sprinkled on applesauce and stored for up to 6 hours in refrigerator[11] • Due to COX-2 selectivity, preferred NSAID in patients with impaired clotting or who receive anticoagulants[21]	Y
Diclofenac (Voltaren, Cambia)[11,16]	Initial: 2-3mg/kg PO divided BID-TID MDD: 150mg/day	Oral packet (Cambia): 50mg Tablet (DR)*: 25mg, 50mg, 75mg Tablet(ER)*: 100mg Tablet (IR): 50mg	**Diclofenac** • Food may decrease absorption; however, may take with food or milk to reduce GI upset • Packets are brand only and expensive • Packet contents should be mixed with 1-2 ounces of water to yield 50mg/30ml or 50mg/60ml mixtures. Mix well and give right away. Doses less than 50mg can be derived, but remainder of mixture should be discarded.	Y/N*
Ibuprofen (Advil, Motrin, Caldolor)[2,17-18]	Initial (PO): <u>≥6 months old (see notes)</u> 4-10mg/kg/dose Q6-8 hours Initial (IV): <u>≥6 months old (see notes)</u> 10mg/kg/dose Q4-6 hours MDD (PO/IV): 40mg/kg or 2,400mg/day	Chewable tablet: 100mg Oral solution: 100mg/5ml, 50mg/1.25ml Solution for injection: (Caldolor): 800mg/200ml IV solution, 100mg/ml vial Tablet: 200mg, 400mg, 600mg, 800mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)				
Indomethacin (Indocin)[16]	Initial: ≥6 months old 1—2mg/kg/day PO divided BID-QID MDD: 4mg/kg or 200mg/day	Capsule: 25mg, 50mg Oral suspension: 25mg/5ml Suppository: 50mg	**Ibuprofen** • NSAID of choice in pediatric patients due to safety data, dosage form flexibility, and cost • Typically reserved for infants ≥6 months old, but can consider use in infants as young as 3 months old as long as weight ≥5kg and no heart or renal disease[8] • Note: ibuprofen lysine (NeoProfen; not listed) is not used for pain treatment **Indomethacin** • Suppositories, oral suspension, and solution for injection are expensive **Ketorolac** • 60mg/2ml vial (for IM use only) not recommended for use in pediatrics due to high dose • Boxed warning: for short-term use only (see dosing) • Solution for injection could be administered orally to provide small, non-commercially available doses **Naproxen** • 275mg sodium formulation is equivalent to 250mg naproxen base[11] • Suspension is expensive	Y/N*
Ketorolac (Toradol)[2,17-18]	Initial (PO): ≥2 years old 1mg/kg x1 dose, not to exceed 10mg/dose Initial (IV/IM): 0.3-0.5mg/kg Q6-8 hours, not to exceed 30mg/dose MDD (PO): 10mg/day (only single dose oral regimens have been studied) MDD (IV/IM): 90mg/day Max Duration: ≤2 years old: 3 days >2 years old: 5 days	Solution for injection:15mg/ml, 30mg/ml, Tablet: 10mg		Y
Naproxen (Aleve, Naprosyn)[2,17-18]	Initial: ≥2 years old & <60kg: 5-10 mg/kg/dose PO Q8-12 hours ≥60kg: 250mg-375mg PO Q12 hours MDD: 1,000mg/day	Capsule (sodium): 220mg Oral suspension: 125mg/5ml Tablet (base): 250mg, 375mg, 500mg Tablet (ER, sodium)*: 375mg, 500mg Tablet (sodium): 220mg, 275mg, 550mg		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
STEROIDS				
Dexamethasone (Decadron)[2-3,11]	Initial: 1-2mg/kg load then 1mg/kg/day PO/ IV/IM divided Q4-6 hours MDD:16mg/day (maintenance)	Tablet: 0.25mg, 0.5mg, 0.75mg, 1mg, 1.5mg, 2mg, 4mg, 6mg Oral solution: 0.5mg/5ml, 1mg/ml Solution for injection: 4mg/ml, 10mg/ml	**Steroids** • May cause GI upset; take with food or milk[2] • If long term use, withdraw slowly[13] **Dexamethasone** • May give 10mg/ml (PF) IV formulation orally	Y
Prednisone (Deltasone)[2,11]	Initial: 0.5-1mg/kg/day PO divided Q12-24 hours MDD: 40mg/day	Tablet: 1mg, 2.5mg, 5mg, 10mg, 20mg, 50mg	**Prednisolone** • Prednisone and prednisolone have a 1:1 equivalency • 3mg/ml oral solution is most cost-effective dosage form	Y
Prednisolone (Orapred)	Initial: 0.5-1mg/kg/day PO divided Q12-24 hours MDD: 40mg/day	Oral syrup: 1mg/ml, 2mg/ml, 3mg/ml, 4mg/ml, 5mg/ml Tablet (ODT): 10mg, 15mg, 30mg		N
OPIOID ANALGESICS				
Fentanyl (Duragesic, Sublimaze)[2-3,11,16,18]	Initial (IV/SQ): ≤50 kg: 0.5-2mcg/kg Q1-2 hours ≥50 kg: 25-50mcg Q1-2 hours Initial (IV/SQ infusion): Variable based on current opioid usage. Should be reserved for opioid tolerate patients. Initial (transdermal): Based on typical immediate release use; patient should be tolerant to at least 30mg oral morphine or equivalent [5,22]	Solution for injection: 0.05mg/mL (50mcg/ml) Transdermal patch: 12mcg/hr, 25mcg/hr, 37.5mcg/hr, 50mcg/hr, 62.5mcg/hr, 75mcg/hr, 87.5mcg/hr, 100mcg/hr	**Opioids** • Cause constipation; prophylactic bowel care recommended • May cause nausea and vomiting, especially upon therapy initiation • Administer with food or milk to decrease GI upset **Fentanyl** • Exercise caution when dosing, double-checking units • Fentanyl safety has not been established in patients <2 years of age • Patches may have increased absorption in febrile patients and young children[11] • Patches should be applied to upper back to limit patient ability to reach / touch patch[13] • Do not cut patches	NA
Hydrocodone / acetaminophen (Norco, Lortab, Lorcet)[2,11]	Initial: <50kg: 0.1-0.2mg/kg PO Q4-6 hours ≥50kg: 5-10mg PO Q4-6 hours MDD: 75mg/kg/day of APAP	Oral solution: 7.5/325mg/15ml, 10mg/325mg/15ml Tablet: 5mg/325mg, 7.5mg/325mg, 10mg/325mg	• Caution with CYP3A4 inhibitors and inducers[16] • 37.5mcg/hr, 62.5mcg/hr, 87.5mcg/hr patch strengths are disproportionately expensive • Due to age and weight requirements, nasal spray and lozenges not appropriate for most pediatric patients *(Continued on next page)*	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OPIOID ANALGESICS (CONTINUED)				
Hydromorphone (Dilaudid, Exalgo)[2,17-18]	Initial (PO): <u>≥6 months old & 10-50kg:</u> 0.03-0.08 mg/kg PO Q3-4 hours (max 2mg/dose) <u>≥50kg:</u> 1-2mg PO Q3-4 hours Initial (IV/SQ): <u>≥6 months old & <50kg:</u> 0.01-0.015 mg/kg Q3-6 hours <u>≥50kg:</u> 0.2-0.6mg Q2-4 hours Initial (IV/SQ infusion): <u><50kg:</u> 0.003-0.005mg/kg/hour (max 0.2mg/hour) <u>≥50kg:</u> 0.3mg/hour	Oral solution: 1mg/ml Solution for injection: 0.2mg/ml, 1mg/ml, 2mg/ml, 4mg/ml, 10mg/ml Tablet (IR): 2mg, 4mg, 8mg Tablet (ER)*: 8mg, 12mg, 16mg, 32mg	**Hydrocodone** • Dosing is based on hydrocodone component but, MDD limited due to acetaminophen component • Combination agent; not 1st line therapy • Caution with CYP3A4 inhibitors, may increase drug concentration[11] **Hydromorphone** • ER formulations are not FDA approved for pediatric use[7] **Methadone** • Use with caution; may accumulate due to long half-life • High interpatient variability in absorption, metabolism, and relative analgesic potency[16] • The first 2-3 doses may be administered Q4-6 hours to improve pain control, then extend the dosing interval to Q8-12 hours[17] • Effective for both nociceptive and neuropathic pain[2,11] • Many drug interactions; double check when initiating or adjusting drug regimens **Morphine** • Opioid of choice in pediatrics[3] • Caution in renal failure • Avinza and Kadian (ER formulations) are dosed Q24 hours[11] • ER capsule dosage forms may be opened, but contents should not be crushed or administered through gastric or nasogastric tubes **Oxycodone** • Children may have faster clearance and lower volume of distribution requiring higher doses than expected[23] *(Continued on next page)*	Y/N*
Methadone (Dolophine, Methadose)[2,17]	Initial (PO): <u>≤6 months old:</u> 0.025-0.05mg/kg Q8-12 hours (see comments) <u>>6 months & <50kg:</u> 0.1-0.2mg/kg Q8-12 hours (see comments) <u>≥50kg:</u> 5-10mg Q8-12 hours (see comments) Initial (IV/SQ): <u>≤ 6 months old:</u> 0.025mg/kg Q6-12 hours <u>>6 months & <50kg:</u> 0.1mg/kg/dose Q6-12 hours <u>≥50kg:</u> 5-8mg Q6-12 hours	Oral solution: 1mg/ml, 2mg/1ml, 10mg/ml Solution for injection: 10mg/ml Tablet: 5mg, 10mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OPIOID ANALGESICS (CONTINUED)				
Morphine Sulfate (Roxanol, MS Contin, Kadian)[2,3,18]	Initial (PO, IR): <u>≤6 months old:</u> 0.08-0.1mg/kg Q3-4 hours <u>≥6 months and <50kg:</u> 0.2-0.3mg/kg Q3-4 hours <u>≥50kg:</u> 10-15mg Q3-4 hours Initial (PO, ER): Based on typical immediate release use; patient should be tolerant to at least 10mg (if using 24-hour capsule) or 30mg (if using 12-hour tablet) of oral morphine or equivalent.[2] Initial (IV/SQ): <u>≤6 months old:</u> 0.025-0.03mg/kg Q2-4 hours <u>>6 months and <50kg:</u> 0.05mg/kg Q2-4 hours <u>≥50kg:</u> 2-5mg Q2-4 hours	Capsule (ER-24hour): 10mg, 20mg, 30mg, 40mg, 45mg, 50mg, 60mg, 75mg, 80mg, 90mg, 100mg, 120mg, 200mg Oral solution: 2mg/ml, 4mg/ml, 20mg/ml Solution for injection: Numerous concentrations available, ranging from 0.5 to 50mg/ml Tablet: 15mg, 30mg Tablet (ER-12hour)*: 15mg, 30mg, 60mg, 100mg, 200mg		Y/N*
Oxycodone (Roxicodone, Oxycontin)[2,11,16]	Initial (IR): <u>≤6 months old:</u> 0.025-0.05mg/kg PO Q4-6 hours <u>>6 months & <50kg:</u> 0.1-0.2mg/kg PO Q4-6 hours <u>≥50kg:</u> 5-10mg PO Q4-6 hours Initial (ER): Based on typical immediate release use; patient should be tolerant to at least 30mg oral morphine or equivalent.[2]	Oral solution: 1mg/ml, 20mg/ml Tablet: 5mg, 10mg, 15mg, 20mg, 30mg Tablet (ER)*: 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
TRICYLCLIC ANTIDEPRESSANTS (TCAS)				
Amitriptyline (Elavil)[2-3,17]	Initial: 2-12 years old: 0.1mg/kg PO QHS >12 years old: 10-25mg QHS MDD: 2-12 years old: 0.5-2mg/kg QHS >12 years old: 150mg/day	Tablet: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	**TCAs** • Boxed warning due to increased suicide and depression risk in children and young adults[11] • Can take 1-3 weeks for full analgesic effects[11] • Once daily doses should be given at bedtime due to sedative effect[3] • Do not discontinue abruptly[2] **Amitriptyline** • Most anticholinergic TCA **Desipramine** • Titrate dose slowly every few days up to target dose of 3.5mg/kg/day[2,16] • Give with food to decrease GI upset[11] **Desipramine & Nortriptyline** • Least anticholinergic TCAs **Nortriptyline** • Liquid dosage form convenient for pediatric patients	Y
Desipramine (Norpramin)[2]	Initial: ≥12 years old 1.5mg/kg/day divided Q12 hours MDD: 150mg/day	Tablet: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg		Y
Nortriptyline (Pamelor)[2,17]	Initial: 0.05-1mg/kg PO QHS MDD: 3mg/kg/day or 50mg/day	Capsule: 10mg, 25mg, 50mg, 75mg Oral solution: 10mg/5ml		Y
GABAPENTINOIDS				
Gabapentin (Neurontin, Gralise)[17]	Initial: day 1-3: 2mg/kg PO TID day 4-6: 4mg/kg PO TID day 7-9: 6mg/kg PO TID day 10-12: 8mg/kg PO TID MDD: <5 years: 72mg/kg (3,600mg) (see comments) ≥5yr: 50mg/kg/day (2,400mg) (see comments)	Capsule: 100mg, 300mg, 400mg Oral solution: 50mg/ml Tablet: 600mg, 800mg	**Gabapentinoids** • Even in patients without seizure history, do not discontinue abruptly because seizure and other withdrawal effects can occur **Gabapentin** • Better safety profile and less expensive than pregabalin • Paradoxically, patients less than 5 years old may require higher doses (see MDDs)[17] • Doses up to 3,600mg per day are used, however doses greater than 2,400mg have incrementally less benefit due to decreased bioavailability • Increase until effective analgesia is reached • Do not give within 2 hours of magnesium or aluminum containing antacids because they decrease gabapentin bioavailability. It is not known if this applies to other polyvalent cations (eg, iron, zinc).[11,18] **Pregabalin** • IR capsules and oral solutions available in generic, ER capsules are brand only and more expensive	Y
Pregabalin (Lyrica)[17]	Initial: day 1-3: 1mg/kg PO QHS (max 50mg) day 4-6: 1mg/kg PO Q12 hours Increase every 2-4 days to target of 3mg/kg/dose PO Q8-12 hours MDD: 14mg/kg/day (600mg)	Capsule: 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg Capsule (ER)*: 82.5mg 165mg, 330mg Oral solution: 20mg/ml		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICHOLINERGICS				
Dicyclomine (Bentyl)[11]	Initial: <u>>6 months old:</u> 5mg PO Q6-8 hours <u>>2 years old:</u> 10mg PO Q6-8 hours MDD: Same as initial dosing	Capsule: 10mg Oral Solution: 2mg/ml Tablet: 20mg	• For infants and young children, diluting the oral solution 1:1 with water can improve bitter flavor[11]	Y
Hyoscyamine (Levsin, Hyomax-SL)[11]	Initial: <u><2 years old:</u> <u>3.4-5kg:</u> 4 drops (0.01375mg) PO/SL Q4 hours PRN <u>5-7kg:</u> 5 drops (0.0175mg) PO/SL Q4 hours PRN <u>7-10kg:</u> 6 drops (0.02mg) PO/SL Q4 hours PRN <u>≥10kg:</u> 8 drops (0.0275mg) PO/SL Q4 hours PRN <u>2-12 years old:</u> 0.0625-0.125mg PO/SL Q4 hours PRN MDD: same as initial dosing	Tablet: 0.125mg Tablet (ODT): 0.125mg Oral solution: 0.125mg/ml	• Use the dropper that comes with the package, which is marked with specific graduations; 3, 4, or 5 drops or 0.25ml • For the 0.125mg/ml solution, 1ml contains about 36 drops of solution when using the dropper from the package	Y
ANTI-SPASTIC AGENTS				
Baclofen (Lioresal, Ozobax)[2]	Initial: <u><2 years old:</u> 2.5mg PO QD <u>2-7 years old:</u> 5mg PO QD <u>>8 years old:</u> 5mg PO QD MDD: <u><2 years old:</u> 40mg/day <u>2-7 years old:</u> 60mg/day <u>>8 years old:</u> 80mg/day	Oral solution: 5mg/5ml Tablet: 10mg, 20mg	• Baclofen should be initiated once daily and additional doses should be added as tolerated up to TID[24] • Taper if discontinuing, due to risk of withdrawal[2] • Injection is for intrathecal use only • Rare cases of baclofen doses >80mg have been used, but must be titrated cautiously[25] • Oral solution is expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTI-SPASTIC AGENTS (CONTINUED)				
Tizanidine (Zanaflex)[1,17,31]	**Spasticity** Initial: 0.3mg/kg/day PO divided TID-QID MDD: 24mg/day	Capsule: 2mg, 4mg, 6mg Tablet: 2mg, 4mg	• Taper if discontinuing, due to risk of withdrawal • Administer consistently with or without food • Effects of administering with food on bioavailability and onset of action varies by dosage form; products may not be directly interchangeable	Y
OTHER				
Acetaminophen (Tylenol)[2,11,17]	Initial (PO/IV): <2 years: 7.5mg/kg/dose Q6 hours >2yrs & <50kg: 10-15mg/kg/dose Q4-6 hours >50kg: 500-1,000mg Q4-6 hours Initial (PR): 10-20mg/kg/dose Q4-6 hours (max 5 doses/day)[2] MDD: 75mg/kg/day or 4,000mg/day	Chewable tablet: 80mg, 160mg Geltab*: 500mg, 650mg Oral solution: 160mg/5ml Solution for injection: 10mg/ml Suppository: 80mg, 120mg, 325mg, 650mg Tablet: 325mg, 500mg Tablet (ER)*: 650mg	• Can be used along with NSAIDs or opioids • Lacks anti-inflammatory effects[13] • Rectal dosing is slightly higher than oral due to variable absorption • Concentrated Infant drops (80mg/0.8ml) are no longer available. Currently, products labeled as infant drops are 160mg/5ml	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER (CONTINUED)				
Clonidine (Catapres, Kapvay)[11,16,26]	Initial (PO): 1-2mcg/kg/dose PO QD Increase in 1-2mcg/kg/dose increments as blood pressure allows Initial (transdermal): based on stable 24-hour oral dose (see comments) Typical dose max *(relative)*: 200mcg/dose, 24mcg/kg/day or as tolerated	Tablet: 0.1mg, 0.2mg, 0.3mg Tablet (ER)*: 0.1mg Transdermal patch: 0.1mg/24h, 0.2mg/24h, 0.3mg/24h Extemporaneously compounded suspension (20mcg/ml): Crush thirty 0.2mg clonidine tablets (or equivalent amount of other strength), then add 4ml purified water to form a paste. Slowly mix paste with 150ml simple syrup, then QS to 300ml with simple syrup.[27-29]	• Exercise caution when dosing. Double-check units. • IR and ER formulations are not interchangeable[11] • Medication must be tapered and not abruptly discontinued to avoid rebound hypertension[11] • Extemporaneously compounded suspension allows dosing flexibility and is stable for up to 28 days when stored in an amber bottle with refrigeration[27-29] • May switch to transdermal patch when oral dose is titrated to a stable dose (0.3mg/24h patch ≈ 0.1mg PO TID) • Transdermal dose approximately equivalent to total oral daily dose and is applied every 7 days • May change patch every 5 days if effects are noted to wear off prior to day 7[16] • Patches should be applied to clean, and hairless skin free of wounds, away from skin folds[11] • Patches should be applied to upper back to limit patient ability to reach / touch patch[13] • May apply transparent film dressing (eg, Tegaderm) below patch in order to administer a partial dose	Y/N*
Ketamine[17-18,26]	Initial (PO): 0.25mg/kg PO once as test of tolerability MDD: 1mg/kg Q6-8 hours	Solution for injection: 10mg/ml, 50mg/ml, 100mg/ml	• Subanesthetic/sub-dissociative doses are used for analgesic purposes • Not first-line therapy; should be used by a practitioner who is familiar with use • For oral administration may compound or use the IV solution[11] • Give an initial one-time dose to test tolerance, effect on pain, and duration of effect. Then may increase up to 3-4 times/day and titrate dose as tolerated. • Likely has an opioid-sparing effect. Can potentially reverse opioid-induced hyperalgesia and allodynia. Caution if a patient is on high opioid doses; consider pre-emptive opioid dose reduction.[26] • Side-effects: hallucinations, excessive salivation, nausea / vomiting and undesirable psychological manifestations[11,18,26] • Benzodiazepines can be used to treat psychiatric adverse effects[26]	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Lidocaine (Lidoderm, Xylocaine)[2,11,17]	Initial (patch): Apply up to 1 patch topically for 12 hours on & 12 hours off. Initial (Cream/ointment/ jelly): Apply a thin film to affected area up to TID-QID. MDD (patch): 1 patch MDD (cream/ointment / jelly): 4.5mg/kg/dose	Cream: 3% 4%, 5% Ointment: 5% Patch: 4%, 5%	• Use smallest effective amount, especially in younger patients[16] • May cut patches prior to removing backing • Can be used synergistically with TCAs or gabapentinoids • OTC 4% patches are less expensive than Rx 5% patches and provide similar pain control	-

References

1. Merskey H, Bogduk N, Part III: Pain Terms, A Current List with Definitions and Notes on Usage" (pp 209-214) Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy. Seattle, WA. IASP Press, 1994.
2. Shega JW, Paniagua MA. Pediatric Palliative Care and Hospice: Essential Practices in Hospice and Palliative Medicine. Chicago, IL: AAHPM; 2017.
3. Goldman A, Hain R, Liben S. Oxford Textbook of Palliative Care for Children. Oxford: Oxford University Press; 2012.
4. Crosta QR, Ward TM, et al. A review of pain measures for hospitalized patients with cognitive impairment. J Spec Pediatr Nurs. 2014;19 (2):109-18.
5. Zernikow B, Michel E, Anderson B. Transdermal fentanyl in childhood and adolescence a comprehensive literature review. J Pain. 2007; 8(3): 187-207
6. Wong C. Lau E, et al. Pain management in children: Part 1-Pain assessment tools and a brief review of nonpharmacological and pharmacological treatment options. Can Pharm J (Ott). 2012; 145 (5):222-5.
7. WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. (2012).
8. Ziesenitz, V. C., Zutter, A., Erb, T. O., & Anker, J. N. V. D. (2017). Efficacy and Safety of Ibuprofen in Infants Aged Between 3 and 6 Months. Pediatric Drugs, 19(4), 277–290. doi: 10.1007/s40272-017-0235-3
9. Smith C, Goldman RD. Alternating acetaminophen and ibuprofen for pain in children. Can Fam Physicians. 2012; 58 (6): 645-647.
10. FDA. "FDA restricts use of prescription codeine pain and cough medicine and tramadol pain medicines in children; recommends against use in breastfeeding women." Last modified March 8, 2018. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-restricts-use-prescription-codeine-pain-and-cough-medicines-and
11. https://online-lexi-com.mwu.idm.oclc.org/lco/action/home
12. Matzo, Marianne, and Katherine A. Dawson. "Opioid-Induced Neurotoxicity." AJN, American Journal of Nursing, vol. 113, no. 10, 2013, pp. 51–56., doi:10.1097/01.naj.0000435351.53534.83.
13. Schechter NL, Berde CB, Yaster M. Pain in infants, children, and adolescents. Philadelphia, PA. Lippincott Williams & Wilkins, 2003.
14. Rasmussen, Lisa Ann, and Marie-Claude Grégoire. "Challenging Neurological Symptoms in Paediatric Palliative Care: An Approach to Symptom Evaluation and Management in Children with Neurological Impairment." Paediatrics & Child Health, vol. 20, no. 3, 2015, pp. 159–165., doi:10.1093/pch/20.3.159.
15. Blackman JA, Patrick PD, Buck ML. "Paroxysmal Autonomic Instability with Dystonia after Brain Injury". Arch Neurol. 2004; 61(3): 321-28.
16. Hauer J, Houtrow AJ, AAP Section on Hospice and Palliative Medicine, Council on children with Disabilities. Pain Assessment and Treatment in Children With Significant Impairment of the Central Nervous System. Pediatrics. 2017;139(6):e20171002.
17. https://www-uptodate-com.mwu.idm.oclc.org/contents/search
18. Hauer J, Duncan J, Scullion BF. Pediatric pain and symptom management guidelines. In: Team PAC, editor. Boston Children's Hospital Dana Farber Cancer Institute. 2014.
19. Donnelly, R. et al. Stability of Celecoxib oral suspension; *Can J Hosp Pharm*, 62(6):464-68.
20. https://neofax-micromedexsolutions-com.mwu.idm.oclc.org/neofax/neofax.php?navitem=topNeoFax
21. Gladding PA, Webster MWI, et al. The Antiplatelet effect of six non-steroidal antiinflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. Am J Cardiol. 2008; 101 (7): 1060-3.
22. Duragesic [package insert]. Titusville,NJ 08560: Janssen Pharmaceutica Products, L.P.; 2003.
23. Friedrichsdorf, S. J., & Kang, T. I. (2007, October 12). The Management of Pain in Children with Life-limiting Illnesses. Retrieved from https://www.sciencedirect.com/science/article/pii/S0031395507001162.
24. Scheinberg A, Hall K, et al. Oral baclofen in children with cerebral palsy: A double-blind cross-over pilot study. J Paediatr Child Health. 2006; 42 (11): 715-20.
25. Lubsch L, Habersang R, et al. Oral Baclofen and clonidine for treatment of spasticity in children. J Child Neurol. 2006 Dec;21(12):1090-2.
26. Splinter, W. Novel Approaches for Treating Pain in Children. Curr Oncol. Rep. 2019; 21 (2): 11.
27. Pesko, LI, Compounding: Clonidine Oral Liquid, *Am Druggist*, 1992; Apr: 68.
28. Levinson ML, et al. Stability of an extemporaneously compounded clonidine hydrochloride oral liquid, *Am J Hosp Pharm*, 1992; 49(Jan): 122-5.
29. Nationwide Children's Hospital – Pharmacy Department; Clonidine 20mcg/ml oral suspension; accessed online Dec 2020 at: file:///C:/Users/jsolien/Downloads/Clonidine%20Oral.pdf
30. Bredlau A, McDermott MP, et al. Oral ketamine for children with chronic pain: a pilot phase 1 study. J Pediatr. 2013; 163(1):194-200
31. Zanaflex. [Package insert]. Ardsely, NY 10502: Acord Therapeutics Inc; 2013.

Pediatric Seizure

DEFINITIONS[1,5-6]

Seizure: transient, abnormal, excessive or synchronous neuronal activity in the brain with resultant signs and/or symptoms

Epilepsy: disorder of the brain characterized by an enduring predisposition to generated epileptic seizures. One of the following conditions must be met:

- 2 unprovoked seizures occurring greater than 24 hours apart
- 1 unprovoked seizure and a probability of future seizures being greater than 60%
- Diagnosis of an epilepsy syndrome

Epilepsy syndrome: a cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together

Pharmacoresistant (drug resistant) epilepsy: failed trials of appropriately selected / dosed and well-tolerated antiseizure drug agents, whether used as monotherapy or in combination, to achieve sustained seizure freedom

Prolonged seizure: seizure lasting between 5 and 30 minutes

Status epilepticus: greater than 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures; may lead to permanent neuronal injury.

HOW TO RECOGNIZE SYMPTOMS[3,4]

- Change of consciousness, responsiveness, or behavior
- Motor movement
  - Clonic: sustained rhythmic jerking. Can be symmetric or asymmetric
  - Tonic: stiffening
  - Myoclonic: sudden, brief involuntary contraction of a muscle or group of muscles
    - Eyelid myoclonia: brief and repeated myoclonic jerks of the eyelids, eyeballs roll upwards, and head may move slightly backwards.[7]
  - Atonic: sudden loss or diminution of muscle tone. May be a head drop, limb, or whole body
  - Absence: sudden cessation of activity and awareness
  - Epileptic spasm: sudden flexion, extension, or missed extension-flexion of proximal and truncal muscles, generally cluster. More sustained than a myoclonic movement, but not as much as a tonic seizure
  - Automatisms: semi-coordinated, repetitive motor activities that are associated with impaired awareness and occur in both focal and generalized seizures. They may manifest as a continuation of activity begun prior to seizure or as a new activity after seizure begins.[8]

NOMENCLATURE AND CLASSIFICATION OF SEIZURES

- Seizures are classified first by onset (focal, generalized, or unknown), then by awareness level and motor characterization.
- Focal onset seizures (previously known as partial seizure) involve part of the brain.
  - Aware or impaired awareness (previously known as simple partial and complex partial, respectively)
  - Motor onset: automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, tonic
  - Non-motor onset:
    - Automatisms: relatively coordinated motor activity that resembles voluntary movement but occurs when cognition is impaired and may continue or repeat inappropriately
    - Behavior arrest: cessation of movement or thought
    - Cognitive and emotional: change in thought, feeling, or experiences (eg, memory impairment, inability to find the correct word, déjà vu, jamais vu)
    - Sensory: sudden strong, often inappropriate emotion (eg, feeling of floating or spinning, hearing sounds, smelling or tasting things)

- Generalized seizures involve the whole brain and impair consciousness.
  - » Motor onset: tonic-clonic (previously known as grand mal), clonic, tonic, myoclonic, myoclonic-tonic-clonic, myotonic-atonic, atonic, epileptic spasms
  - » Non-motor onset: absence (previously known as petite mal), typical, atypical, myoclonic absence, eyelid myoclonia
- Unknown onset seizure
  - » Motor onset: tonic-clonic, epileptic spasms
  - » Non-motor onset: behavior arrest
  - » Unclassified
- Dynamic nature of seizures
  - » Seizures can start as focal, but then evolve to generalize the whole brain
  - » Focal seizures can progress to impaired awareness / consciousness

CAUSES[2,3]

- Of seizures (select)
  - » Epilepsy
  - » Acquired
    - ° Brain tumors / metastases
    - ° CNS Infection
    - ° Head injury / trauma
  - » Metabolic / physiologic
    - ° Fever
    - ° Hypoglycemia
    - ° Hypoxia
    - ° Metabolic or electrolyte disturbances
    - ° Stroke / TIA
    - ° Sleep deprivation
    - ° Encephalopathy
      - › Renal failure
      - › Liver cirrhosis
  - » Iatrogenic
    - ° Medications
    - ° Drug withdrawal / abrupt discontinuation (eg, anticonvulsants, benzodiazepines, opioids, sedatives, alcohol)
- Of epilepsy
  - » Structural: stroke, trauma, infection, genetic malformation of cortical development predispose patients to seizures
    - ° Examples: genetic mutation that leads to polymicrogyria, intrauterine stroke leading to ischemia, congenital CMV leading to cortical malformation
  - » Genetic: epilepsy results directly from known or presumed genetic mutation where seizures are a core symptom of the disorder
    - ° Examples: patients with SCN1a mutation that develop Dravet syndrome
  - » Infectious: epilepsy occurs as a result of infection and seizures are a core symptom of the disorder. This excludes seizures in the acute setting of infection such as meningitis and encephalitis
    - ° Examples: cerebral toxoplasmosis, congenital Zika virus and CMV
  - » Metabolic: epilepsy develops as a result of known or presumed metabolic disorder where seizures are a core symptom of the disorder
    - ° Examples: porphyria, aminoacidopathies, pyridoxine-dependent seizures, folate deficiency (acquired)
  - » Immune: results directly from an immune disorder in which seizures are a core symptom
    - ° Examples: anti-NMDA receptor encephalitis
  - » Unknown: cause of epilepsy is not yet known

CLINICAL INSIGHTS

- Antiepileptic drugs (AEDs) are often FDA-approved for certain age ranges or seizure types. However, many have confirmed efficacy or are likely effective in younger patients or patients with other, non-approved seizure types; as such, off label AED use is common.
  - » Insurance providers often deny coverage of AEDs when prescribed off label.
- Effective AED regimens take time to establish; therefore, medications should generally not be

substituted, adjusted or deescalated in the hospice setting unless a patient, parent, provider believes a medication has not worked or is no longer working.

  - » If an AED is to be discontinued, it should be gradually tapered and not abruptly discontinued, as this can exacerbate seizures.
  - » Due to the potential for subtle potency variability between generic AED manufacturers, patients should use the same generic manufacturer whenever possible to prevent breakthrough seizures or adverse effects.[9]
  - » Clobazam is a structurally unique among benzodiazepines and has different pharmacokinetic properties than other benzodiazepines and lower risk of tachyphylaxis (development of tolerance requiring dose escalation) and sedation. Generally, other benzodiazepines should not be substituted in its place.

- Pharmacoresistant epilepsy frequently requires the use of multiple AEDs and doses higher than FDA-approved. Caution should be exercised with high doses of phenobarbital, phenytoin, and valproic acid, as elevated levels can lead to coma, death, or other toxicities. If exceeding FDA-approved dosing, obtaining levels should be considered if consistent with goals of care.
  - » Therapeutic drug monitoring (TDM) is a standard of care for many AEDs (especially those with narrow therapeutic indexes) in non-hospice patients, but is not a requirement in the hospice setting, as it can decrease quality of life. TDM is reasonable if AED toxicity is suspected.
- Sedation is a common side effect of most AEDs and some are controlled substances.
- Some antiepileptics, including ethosuximide, carbamazepine, oxcarbazepine, and phenytoin can worsen certain seizures types or patients can have an atypical reaction of worsening seizures. If this occurs, they should be discontinued.
- AEDs with primary sodium channel blocking action (lamotrigine, carbamazepine, oxcarbazepine, lacosamide, and phenytoin) can cause dizziness, blurry vision, ataxia, and gait disturbances at higher doses or toxic levels.
- AEDs are disproportionately involved in drug interactions. Interacting medications can often be used concomitantly, but may require dose adjustments and / or closer monitoring. Drug interactions should always be checked when starting or stopping an AED or concomitant medication.
- Most drug interactions involving AEDs are pharmacokinetic in nature, specifically inhibiting or inducing enzymes involved in drug metabolism.
  - » Enzyme inducers: carbamazepine, oxcarbazepine, phenobarbital, primidone, phenytoin
  - » Enzyme inhibitors: stiripentol, valproate
  - » Enzyme inhibitors and inducers: cenobamate, felbamate, rufinamide
  - » Other AEDs are not without drug interactions, but are not broad spectrum inducers or inhibitors
- Patients receiving low-carbohydrate diet therapies for seizures will generally require tablets or capsules instead of liquids to limit carbohydrate count. Certain ER / DR medications can be crushed but are effectively turned into IR dosage forms (eg, divalproex).

STATUS EPILEPTICUS (SE)

- SE is a serious condition which can lead to cardio-respiratory collapse and death.
- Patients with a history of prolonged seizures or long durations of acute repetitive seizures should have a quick acting rescue medication available to prevent transition to SE. Benzodiazepines are the preferred agents due to their efficacy, safety, and tolerability.
- Rescue benzodiazepines are typically given after 5 minutes of seizure activity due to the high likelihood of continuance to SE if seizure continues beyond 5 minutes.[5]

  - » Rescue medication may be given sooner, particularly in patients with high propensity for SE.
  - » For patients with seizure clusters, rescue medication is usually given after 3 clusters or 10-15 minutes of clusters.
  - » The longer the duration of status epilepticus, the lower the chances of successful seizure control.
- Intramuscular midazolam, intravenous lorazepam, and intravenous diazepam have the highest level of supporting evidence for rescue use.
- Because IV access is uncommon in hospice patients and IM injections are generally avoided, alternative options are more commonly used in the hospice setting.
  - » Alternative, evidence-based options are intranasal or buccal midazolam and rectal diazepam (gel or solution for injection via catheter; not suppositories).
  - » Intranasal midazolam, using an injectable formulation (with a nasal atomizer, when possible) or commercially available intranasal spray is the preferred option in most cases.
- If patient continues to seize after 2 doses of benzodiazepines, they can be referred for emergency care if consistent with goals of care and family wishes.

NON-PHARMACOLOGIC THERAPIES

- Patients may require a combination of pharmacologic and non-pharmacologic therapies to control seizures.
- Common non-pharmacologic therapies include:
  - » Dietary therapy: ketogenic, modified Atkins
  - » Surgery: vagal nerve stimulator, corpus callosotomy, focal resection, deep brain stimulation, responsive neurostimulation

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Acetazolamide (Diamox)[9]	Initial: 4mg/kg/day PO in 1-2 divided doses OR 250mg/dose, whichever is less MDD: 30mg/kg/day in 2-4 divided doses or 1,000mg/day, whichever is less (see comments)	Capsule (ER)*: 500mg Tablet: 125mg, 250mg	• Minimal additional benefit with doses > 16mg/kg/day • Administer with food to decrease GI upset • Contraindicated in patients with severe renal or hepatic impairment	Y/N*
Brivaracetam (Briviact)[9]	Initial: 11-19kg: 1-2.5mg/kg/day PO in 2 divided doses 20-49kg: 1-2mg/kg/day PO in 2 divided doses ≥50kg: 25-50mg PO Q12 hours OR 50mg BID, whichever is less MDD: 11-19kg: 5mg/kg/day 20-49kg: 4mg/kg/day ≥50kg: 200mg/day	Oral solution: 10mg/ml Solution for injection: 10mg/ml Tablet*: 10mg, 25mg, 50mg, 75mg, 100mg	• Dose adjustments required in hepatic impairment • FDA-approved for partial (focal) seizures, but it is a broad spectrum antiepileptic similar to levetiracetam • FDA-approved 4 years and older, but off label use for younger children is appropriate • *Tablet is film coated and not recommended to be crushed by manufacturer, but can be cut / crushed if oral solution is unavailable	Y*
Cannabidiol (Epidiolex)[9]	Initial: 5mg/kg/day PO in 2 divided doses MDD: see comments	Oral solution: 100mg/ml	• Dose adjustments required in hepatic impairment • Administer consistently either with or without food • Medication should be administered with manufacturer specific syringe only • Maximum FDA-approved dosing is 20mg/kg/day for Dravet and Lennox-Gastaut syndromes and 25mg/kg/day for seizures due to Tuberous Sclerosis; however additional data exists for dosing up to 50mg/kg/day • Likely a broad spectrum AED with efficacy beyond the above labeled indications • Limited distribution: dispensed by licensed specialty pharmacies in partnership with the drug manufacturer	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Carbamazepine (Tegretol, Carbatrol, Equetro)[9]	Initial: 10-15mg/kg/ day PO in 2-3 divided doses MDD: ≤15 years old: 1,000mg/day OR 35mg/kg/day, whichever is less >15 years: 1,200mg/day	Capsule (ER): 100mg, 200mg, 300mg Chewable tablet: 100mg Oral suspension: 20mg/ml Tablet: 200mg Tablet (ER)*: 100mg, 200mg, 400mg	• Suspension should be given in lower and more frequent doses (TID or QID) than tablets due to higher peak levels / lower trough levels • Boxed warning: toxic epidermal necrolysis (TEN) and Stevens Johnson Syndrome (SJS). Patients of Asian descent should be screened for the HLA-B*15:02 allele prior to starting or avoid use. • Boxed warning: aplastic anemia and agranulocytosis • Induces its own metabolism; may lead to decrease in serum levels after 2-3 weeks requiring dose increase • Capsules may be opened and sprinkled into applesauce, but contents should be swallowed whole • Administer IR doses with food • Use caution in hepatic impairment	Y/N*
Cenobamate (Xcopri)[9]	Initial: 12.5mg PO QD MDD: 400mg/day	Tablet*: 50mg, 100mg, 150mg, 200mg Set titration packs are available	• Only FDA-approved for adult patients, but may be used off-label in pediatric patients • Single report of fatal DRESS. Increase no faster than every 2 weeks. • Can shorten QT interval; use with caution in patients with preexisting arrhythmia or shortened QT • *Tablet is film coated and not recommended to be crushed by manufacturer, but can be crushed if needed	Y*
Clobazam (Onfi, Sympazan)[9]	Initial: ≤30kg: 5mg PO QD or 0.2-0.3mg/kg QD (whichever is less) >30kg: 5mg PO BID or 0.2-0.3mg/kg/day PO in 2 divided doses (whichever is less) MDD: 60mg or 2mg/kg/ day, whichever is less (see notes)	Oral Film: 5mg, 10mg, 20mg Oral suspension: 2.5mg/ml Tablet: 10mg, 20mg	• Apply oral film on tongue, allow to dissolve, swallow normally; do not administer with liquids • Dose adjustments required in hepatic impairment • Use with caution if CrCl <30ml/min. • FDA-approved 2 years and older, but off-label use for younger children is appropriate • FDA-approved maximum dosing is 40mg/day, although 60mg daily is commonly considered the maximum in clinical practice. Additional data exists up to 3.8 mg/kg/day (150mg/day). • FDA-approved for Lennox-Gastaut, but broad spectrum antiepileptic	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Clonazepam (Klonopin)[9]	Initial: 0.01-0.03mg/kg/day PO in 2-3 divided doses MDD: 20mg/day or 0.2mg/kg/day, whichever is less	Oral Disintegrating Tablet (ODT): 0.125mg, 0.25mg, 0.5mg, 1mg, 2mg Tablet: 0.5mg, 1mg, 2mg Extemporaneously compounded suspension (0.1mg/ml): Crush six 2mg tablets to a fine powder and add quantity of vehicle sufficient to make 120ml. Vehicle options are cherry syrup or 1:1 mixture of Ora-Sweet (or Ora-Sweet SF) and Ora-Plus.	• Metabolites may accumulate in renal impairment • Contraindicated in severe hepatic impairment • Compounded oral suspension stable for 60 days at room temperature or refrigerated; store in amber vial; protect from light	Y
Diazepam (Valium, Diastat, Valtoco)[9]	Initial (PO): 0.5mg/kg per dose PRN Initial (IN): 6-11 years old: 0.3mg/kg ≥12 years old: 0.2mg/kg, NTE 20mg/dose Initial (PR): 2-5 years old: 0.5mg/kg 6-11 years old: 0.3mg/kg ≥12 years old: 0.2mg/kg, NTE 20mg/dose Maximum (PO, IN, PR): same as initial dosing per dose; patients requiring more than 2 doses/day should be evaluated clinically.	Oral solution: 1mg/ml, 5mg/ml Prefilled IN device: 5mg, 7.5mg, 10mg Rectal gel: 2.5mg, 10mg, 20mg Solution for injection: 5mg/ml Tablet: 2.5mg, 5mg, 10mg	• Rectal doses should be rounded up to the closest 2.5mg • 10mg rectal gel dosage form can be adjusted to deliver 5mg/7.5mg/10mg doses; 20mg form can deliver 12.5mg/15mg/17.5mg/20mg doses • Compounded rectal suppositories are not appropriate for rescue use due to erratic absorption and low bioavailability[10] • Intranasal formulation FDA-approved 6 years and older	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Eslicarbazepine (Aptiom)[9]	Initial: 5mg/kg PO QD OR weight based tiers below 11-21kg: 200mg PO QD 22-38kg: 300mg PO QD >38kg: 400mg PO QD MDD: 30mg/kg/day, OR weight based tiers below, whichever is less 11-21kg: 600mg/day 22-31kg: 800mg/day 32-38kg: 900mg/day >38kg: 1,200mg/day	Tablet: 200mg, 400mg, 600mg, 800mg	• For treatment of focal seizures • FDA-approved for 4 years and older, but off-label use for younger patients is appropriate • FDA-approved dosing is daily, but younger children may require twice daily dosing • Reduce dose by 50% if CrCl <50ml/min. • Use not recommended in severe hepatic impairment • Chemically related to carbamazepine and oxcarbazepine which are known to cause SJS/TEN. The specific risk has not been determined with eslicarbazepine, but should be used with caution and discontinued if a drug-related rash develops.	Y
Ethosuximide (Zarontin)[9]	Initial: 10mg/kg/day PO in 2-3 divided doses MDD: 2,000mg/day or 60mg/kg/day, whichever is less	Capsule: 250mg Oral solution: 50mg/ml	• Administer with food or milk to decrease GI upset • Use extreme caution in renal and hepatic impairment	N
Felbamate (Felbatol)[9]	Initial: 15mg/kg/day PO in 2-3 divided doses (not to exceed 400mg/dose or 1,200mg/day) MDD: 45mg/kg/day in 3-4 divided doses or 3,600mg/day (see comments)	Oral suspension: 120mg/ml Tablet: 400mg, 600mg	• Boxed warning: aplastic anemia, acute liver failure • Reduce all doses by 50% in renal impairment • Contraindicated in hepatic impairment • Can cause insomnia if given in the evening, so give last dose around dinnertime • FDA-approved for adjunctive therapy for a partial and generalized seizures associated with LGS, but particularly good at treating atonic seizures • FDA-approved up to 45mg/kg/day, but additional data exists up to 100mg/kg/day or a level of 100mcg/ml, whichever is less • FDA-approved dosing is 3-4 times per day, but usually given three times daily for convenience	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Fenfluramine (Fintepla)[9]	Initial: 0.2mg/kg/day PO in 2 divided doses MDD (not receiving stiripentol): 0.7 mg/kg/day or 26mg/day, whichever is less MDD (concomitant stiripentol): 0.35mg/kg/day, 17mg/day, whichever is less	Oral solution: 2.2mg/ml	• Boxed warning: associated with valvular heart disease and pulmonary arterial hypertension • Not recommended in renal or hepatic impairment • FDA-approved for 2 years and older, but off-label use for younger children is appropriate • Only available through restricted access REMS program, requiring prescriber and patient enrollment • Limited distribution: dispensed by a single licensed specialty pharmacy in partnership with the drug manufacturer	-
Fosphenytoin (Cerebyx)[9]	Loading dose: 10-20mg PE/kg IV/IM MDD: 1,500mg PE/dose	Solution for injection: 100mg PE/2ml, 500mg PE/10ml	• PE = phenytoin sodium equivalents • Boxed warning: cardiovascular risk associated with rapid infusion rate; do not exceed 150mg PE/minute • Phenytoin levels may be increased in patients with renal or hepatic impairment; monitor levels more closely if indicated and consistent with goals of care	N/A
Gabapentin (Gralise, Neurontin)[9]	Initial: 10-15mg/kg/day PO in 3 divided doses MDD: 50mg/kg/day or 3,600mg/day, whichever is less	Capsule: 100mg, 300mg, 400mg Oral Solution: 50mg/ml Tablet: 300mg, 600mg, 800mg	• Not recommended to administer within 2 hours of magnesium- or aluminum-containing antacids because it decreases bioavailability. It is not known if this applies to other polyvalent cations (eg, iron, zinc). • Increases risk of respiratory depression when administered with opioids • Dose adjustments required in renal impairment	Y
Lacosamide (Vimpat)[9]	Initial: 1-2mg/kg/day PO in 2 divided doses (not to exceed 50mg/dose) MDD: 15mg/kg/day or 400mg/day, whichever is less (see comments)	Oral solution: 10mg/ml Solution for injection: 200mg/20ml Tablet: 50mg, 100mg, 150mg, 200mg	• Reduce dose to 75% of MDD if CrCl < 30ml/min or mild to moderate hepatic impairment; further reductions may be necessary if taking CYP3A4 or CYP2C9 inhibitors • Use is not recommended in severe hepatic impairment • FDA-approved up to 12 mg/kg/day; additional data exists up to 20 mg/kg/day, but doses >15mg/kg/day are not beneficial in the majority of patients • FDA-approved for 4 years old, but off-label use for younger children is appropriate	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Lamotrigine (Lamictal, Subvenite)[9]	Starting dose and titration varies based on weight and concomitant medications (see **Tables 1&2**) MDD: See **Tables 1&2** below)	Chewable tablet: 5mg, 25mg Oral disintegrating tablet (ODT): 25mg, 50mg, 100mg, 200mg Tablet*: 25mg, 100mg, 150mg, 200mg Tablet (ER)*: 25mg, 50mg, 100mg, 200mg, 250mg, 300mg Various kits available to help with titration schedules Extemporaneously compounded suspension (1mg/ml): crush one 100mg tablet to a fine powder and add quantity of vehicle sufficient to make 100ml. Vehicle is a 1:1 mixture of Ora-Sweet (or Ora-Sweet SF) and Ora-Plus	• Boxed warning: SJS/TEN, which occurs more commonly in children • Use with caution in renal and hepatic impairment; usual maintenance doses may be reduced by ~20-50% • Nausea is the most common side effect (7-14%) • Water or fruit juice may be used to help swallow ODTs and chewable tablets • It is not recommended to crush immediate-release tablets due to bitter taste, which may be especially unpalatable in young children; use chewable or ODT forms instead • There is emerging data on risks of arrhythmia. Higher doses should be used with caution in patients with preexisting arrhythmia, conduction disorders, structural heart disease, or other abnormalities. • Compounded oral suspension is stable for 91 days at room temperature or refrigerated when stored in amber vial and protected from light	Y/N*

TABLE 1. LAMOTRIGINE DOSING IN CHILDREN 2-12 YEARS OLD[9]

	Patients NOT receiving enzyme-inducing regimens or valproic acid#	Patients receiving valproic acid	Patients receiving enzyme-inducing regimens without valproic acid
Weeks 1 & 2	0.3mg/kg/day PO in 1-2 divided doses; round down nearest whole tablet	0.15mg/kg/day PO in 1-2 divided doses; round down nearest whole tablet; use 2mg QOD if needed	0.6mg/kg/day PO in 2 divided doses; round down nearest whole tablet
Weeks 3 & 4	0.6mg/kg/day	0.3mg/kg/day	1.2mg/kg/day
Titration	Increase every 1-2 weeks by no more than 0.6mg/kg/day in 2 divided doses	Increase every 1-2 weeks by no more than 0.3mg/kg/day in 1-2 divided doses	Increase every 1-2 weeks by no more than 1.2mg/kg/day in 2 divided doses
MDD	300mg/day, 10 mg/kg/day	200mg/day, 5 mg/kg/day	400mg/day, 15 mg/kg/day

Common enzyme-inducing therapies that may affect dose or treatment choice of other regimens: phenytoin, phenobarbital, carbamazepine, primidone, rifampin

TABLE 2. LAMOTRIGINE DOSING IN ADOLESCENTS >12 YEARS OLD[9]

	Patients NOT receiving enzyme-inducing regimens or valproic acid#	Patients receiving valproic acid	Patients receiving enzyme-inducing regimens without valproic acid
Weeks 1 & 2	25mg PO QD	25mg PO QOD	50mg PO QD
Weeks 3 & 4	50mg PO QD	25mg PO QD	50mg PO Q12 hours
Titration	Increase every 1-2 weeks by 50mg/day in 2 divided doses	Increase every 1-2 weeks by 25-50mg/day in 2 divided doses	Increase every 1-2 weeks by 100mg/day in 2 divided doses
MDD	375mg/day	400mg/day if receiving other enzyme-inducing drugs 200mg/day if NOT receiving other enzyme-inducing drugs	700mg/day

Common enzyme-inducing therapies that may affect dose or treatment choice of other regimens: phenytoin, phenobarbital, carbamazepine, primidone, rifampin

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Levetiracetam (Keppra, Roweepra, Spritam)[9]	Initial: 10mg/kg/day PO in 2 divided doses (not to exceed 500mg/dose) MDD: 4,000mg/day or 60mg/kg/day (see comments)	Oral disintegrating tablet (ODT): 250mg, 500mg, 750mg, 1,000mg Oral solution: 100mg/ml Solution for injection: 100mg/ml Tablet*: 250mg, 500mg, 750mg, 1,000mg Tablet (ER)*: 500mg, 750mg	• Significantly fewer drug interactions than other AEDs • CNS effects, including behavioral problems and irritability, occur more commonly in children and may be treated by pyridoxine (vitamin B6), which is a treatment option for mood and behavioral problems associated with levetiracetam therapy. Dosing is 10-15 mg/kg/day divided QD-BID; Min: 50mg/day, Max: 200mg/day. • Dose adjustment of 50% has been suggested if GFR <50[2] • FDA-approved up to 60mg/kg/day, but additional data exists up to 100mg/kg/day • Some pediatric patients may metabolize levetiracetam more quickly, warranting TID dosing. This can manifest as breakthrough seizures close to next dosing time / end of dose failure. • *It is not recommended to crush immediate-release tablets due to bitter taste, which may be especially unpalatable in young children; use oral solution instead	Y/N*
Midazolam (Versed, Nayzilam)[9]	Initial (improvised IN/ buccal): 0.2mg/ kg (max: 10mg) of solution for injection per dose Initial (prefilled IN device): 5mg (one actuation/device) after 5 minutes of seizure; repeat dose if seizure continues after another 10 minutes. MDD (both products): 0.3mg/kg/dose (10mg), 2 doses/day given at least 4 hours apart MDD: typically 2 doses/ day, but patient should be evaluated clinically	Prefilled IN device: 5mg/0.1ml per each device/actuation Solution for Injection: 5mg/ml	• Use of 5mg/ml solution for injection for intranasal (IN)/buccal dosing • FDA-approved dosing for prefilled IN device differs from established standard of care using midazolam solution for injection intranasally; may alter prefilled device dosing to mimic IV midazolam dosing if clinically appropriate (ie, use 10mg initial dose) • Prefilled device is not approved for patients >12 years old • Commercially available prefilled IN device is grossly more expensive than using solution for injection IN	

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Oxcarbazepine (Trileptal, Oxtellar XR)[9]	Initial (IR): 10mg/kg/day PO in 2 divided doses Initial (ER): 10mg/kg/day PO QD MDD (all forms): 2,400mg or 60mg/kg/day, whichever is less	Oral suspension: 60mg/ml Tablet: 150mg, 300mg, 600mg Tablet (ER)*: 150mg, 300mg, 600mg	• Extended release and immediate release dosage forms are not bioequivalent; may need to increase ER dose by 16-19%[11] • Fewer drug interactions than carbamazepine • Administer ER tablets on an empty stomach, 1-2 hours before food. Food increases Cmax, but AUC remains the same. This may put patients at risk for adverse effects. • Dose adjustments may be necessary if CrCl <30ml/min • Use caution in severe hepatic impairment • Risk of SJS/TEN. Patients of Asian descent should be screened for the HLA-B*15:02 allele prior to starting or avoid use.	Y/N*
Perampanel (Fycompa)[9]	Initial (Concomitant CYP3A4 inducer use): 2-4mg PO QHS Initial (No concomitant CYP3A4 inducer use): 2mg PO QHS MDD: 12mg/day	Oral suspension: 0.5mg/ml Tablet: 2mg, 4mg, 6mg, 8mg, 10mg, 12mg	• Dose adjustments may be necessary in renal or hepatic impairment • Boxed warning: serious behavioral and psychiatric reactions including dose-related homicidal ideation • FDA-approved for generalized seizures in adults and children 12 years and older, but likely effective in children <12 years as well • FDA-approved for focal seizures in 4 years and older, but off-label use for younger children is appropriate	Y
Phenobarbital[9]	Initial: <u>≤5 years old:</u> 3-5mg/kg/day PO in 1-2 divided doses <u>>5 years old:</u> 2-3mg/kg/day PO in 1-2 divided doses MDD: 6mg/kg/day	Solution for injection: 65mg/ml, 130mg/ml Tablet: 15mg, 16.2mg, 30mg, 32.4mg, 60mg, 64.8mg, 97.2mg, 100mg Extemporaneously compounded alcohol-free oral suspension (10mg/ml): crush ten 60mg tablets to a fine powder and add quantity of vehicle sufficient to make 60ml. Vehicle is a 1:1 mixture of Ora-Sweet (or Ora-Sweet SF) and Ora-Plus	• Commercial elixir and oral solutions contain 15% alcohol; not preferred for children; consider compounded suspension instead (see dosage forms) • OPPC compounds suppositories with ~50% bioavailability. Oral products have an approximately 90% availability. • Use with caution in hepatic impairment • Dose adjustments indicated for severe renal impairment • CNS effects can occur including drowsiness, dizziness, lethargy, and agitation • Compounded oral suspension stable for 115 days when stored in amber vial at room temperature	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Phenytoin (Dilantin, Phenytek)[9]	Initial (IR): 5mg/kg/day PO divided BID-TID Initial (ER): 5mg/kg/day PO divided QD-BID MDD: 300mg/day or 10mg/kg/day, whichever is less; or guided by therapeutic lab monitoring.	Capsule (ER)*: 30mg, 100mg, 200mg, 300mg Chewable tablet: 50mg Oral suspension: 25mg/ml	• Serious dermatologic reactions possible including SJS/TEN. Patients of Asian descent should be screened for the HLA-B*15:02 allele prior to starting or avoid use. • Hold tube feeds 1 hour before and after each dose if possible. Otherwise give consistently with or without feeds. • Younger children typically require higher doses • Use caution at higher doses due to non-linear kinetics • Total phenytoin levels >25mcg/ml higher correlated with toxicity • Monitor free phenytoin levels more closely in patients with renal or hepatic impairment • Doses for capsules (ER) and solution for injection are expressed as phenytoin sodium salt. Doses for oral suspension and chewable tablets are expressed as phenytoin base. (92mg base = 100mg phenytoin sodium). Dose adjustments may be necessary when switching between formulations. • 30mg capsules are only available as branded product	Y/N*
Pregabalin (Lyrica)[9]	Initial (IR): <30kg: 3.5mg/kg/day PO in 2-3 divided doses ≥30kg: 2.5mg/kg/day PO in 2-3 divided doses MDD: <30kg: 14mg/kg/day ≥30kg: 10mg/kg/day or 600mg/day, whichever is less	Capsule: 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg Oral solution: 20mg/ml Tablet (ER)*: 82.5mg, 165mg, 330mg	• Risk of respiratory depression when administered with opioids • Dose adjustment may be necessary in renal impairment	Y/N*
Primidone (Mysoline)[9]	Initial: 50mg-100mg PO QHS MDD: 25mg/kg/day or 2,000mg/day, whichever is less	Tablet: 50mg, 250mg	• Administering with food decreases GI upset • Clearance reduced in patients with renal or hepatic impairment; monitor plasma levels closely when consistent with goals of care	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Rufinamide (Banzel)[9]	Initial: 10mg/kg/day PO in 2 divided doses MDD: 3,200mg/day or 45mg/kg/day, whichever is less	Oral suspension: 40mg/ml Tablet: 200mg, 400mg	• Administer with food • Use with caution in mild-moderate hepatic impairment; contraindicated in severe hepatic impairment • FDA-approved for patients 1 year and older, but use in younger children is appropriate	Y
Stiripentol (Diacomit)[9]	Initial: 10-15mg/kg/day PO in 2 divided doses MDD: 3,000mg/day or 50mg/kg/day, whichever is less	Capsule: 250mg, 500mg Packet: 250mg, 500mg	• Limited distribution: dispensed by a single licensed specialty pharmacy in partnership with the drug manufacturer[12] • Drug levels may vary when switching between powder and capsules • Capsule contents are not soluble in water; mixing with food (eg, yogurt, honey, jam) is preferred[13] • Mix powder packets in 100ml of water and consume immediately. Partial packets may be prescribed by determining corresponding volume of medication based on concentration (2.5 mg/ml or 5mg/ml). • Administer with food • Use with caution in mild renal or hepatic impairment; not recommended in moderate to severe renal or hepatic impairment • FDA-approved for seizures associated with Dravet syndrome in patients 2 years and older, but use is appropriate in younger patients	Y[13]
Topiramate (Topamax, Trokendi, Qudexy)[9]	Initial (IR): 1-3mg/kg/day (up to 25mg/dose) PO QHS; change to 2 divided doses when titrating Initial (ER) (Qudexy): 25mg PO QHS MDD: 400mg/day, 10mg/kg/day; whichever is less	Capsule (ER) (Trokendi)*: 25mg, 50mg, 100mg, 200mg Sprinkle capsule#: 15mg, 25mg Sprinkle capsule (ER) (Qudexy)#: 25mg, 50mg, 100mg, 150mg, 200mg Tablet*: 25mg, 50mg, 100mg, 200mg	• Clearance reduced in setting of renal and hepatic impairment • Avoid alcohol-containing products 6 hours before and after Trokendi administration • *It is not recommended to crush immediate release tablets due to bitter taste, which may be especially unpalatable in young children; use sprinkle capsules instead • #Sprinkle capsules and ER sprinkle capsules may be opened and added to soft food for immediate administration, but contents should be swallowed whole / not chewed. Sprinkles should not be administered via g-tube.	Y#/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Divalproex sodium (Depakote)[9] Valproic Acid (Depakene)[9]	Initial (PO, IR/DR): ≥2 years old: 10-15mg/kg/day in 2-3 divided doses Initial (PR): loading dose of 17-20mg/kg of oral solution as retention enema; then 10-15mg/kg/dose PR Q8 hours[14] MDD (All forms): 60mg/kg/day	Capsule*: 250mg Oral solution: 250mg/5ml Sprinkle capsule (DR)#: 125mg Tablet (DR)*: 125mg, 250mg, 500mg Tablet (ER)*: 250mg, 500mg	• Boxed warning: hepatotoxicity. Children < 2 years old and patients with mitochondrial disease are at highest risk; do not use in this population. • Boxed warning: pancreatitis • Not recommended for use in hepatic impairment • May administer with food to decrease GI adverse effects • Sprinkle capsules may be opened and added to soft food for immediate administration, but contents should be swallowed whole and not chewed. Sprinkles should not be administered via g-tube. • Relative maximum of 60mg/kg/day, but in certain circumstances can increase to 100mg/kg/day if tolerated • ER tablets: » Generally avoided in patients unable to swallow tablets whole » 10% less bioavailable than IR/DR forms; may require dose adjustment when changing forms	Y#/N*
Vigabatrin (Sabril, Vigadrone)[9]	Initial: 30-50mg/kg/day PO in 2 divided doses MDD: 3,000mg/day or 150mg/kg/day, whichever is less	Packet: 500mg Tablet: 500mg	• Boxed warning and REMS: permanent vision loss; monitor frequently • Only available through restricted access REMS program, requiring prescriber and patient enrollment • Dissolve each 500mg packet in 10ml of cold water to make a 50mg/ml solution prior to administration • Additional stability data indicate that prepared solution is stable for up to 24 hours, with or without refrigeration. • Renal dose adjustment if CrCl ≤80ml/min	Y
Zonisamide (Zonegran)[9]	Initial: 1-2mg/kg/day PO in 2 divided doses MDD: 400mg/day or 12mg/kg/day, whichever is less	Capsule: 25mg, 50mg, 100mg	• Clearance decreased in renal impairment; do not use if GFR <50[2] • Slower titration and more frequent monitoring in hepatic impairment	N

References

1. Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. Epilepsia. 2014; 55(4): 475-482.
2. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for the Classification and Terminology. Epilepsia. 2017; 58(4):512-517.
3. Fisher RS, Cross, JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017; 58(4):522-530.
4. Fisher RS, Cross, JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017; 58(4):531-542.
5. Glauser T, Shinnar S, Gloss D, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Currents. 2016; 16(1): 48-61.
6. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010; 51(6):1069-1077.
7. Epilepsy.com; accessed online April 2021 at: https://www.epilepsy.com/learn/types-epilepsy-syndromes/epilepsy-eyelid-myoclonia-jeavons-syndrome
8. Sadleir, L. et al. Automatisms in absence seizures in children with idiopathic generalized epilepsy, Arch Neurol. 2009; 66(6): 729-34.
9. Various Drug Monographs. Lexicomp. Pediatric and Neonatal Lexi-Drugs. Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc. Updated Nov 4-30, 2020. Accessed Nov 17-30, 2020.
10. Rey, Elisabeth, et al. Pharmacokinetic optimization of benzodiazepine therapy for acute seizures – Focus on delivery routes, Clinical Pharmacokinetics, 1999; 36(6): 409-24.
11. Product Information: OXTELLAR XR(R) oral extended-release tablets, oxcarbazepine oral extended-release tablets. Supernus Pharmaceuticals Inc (per FDA), Rockville, MD, 2015.
12. Diacomit Ordering and Support. Biocodex. Accessed December 30, 2020. https://www.diacomit.com/support/
13. Biocodex Medical Information. Diacomit (stiripentol). Personal Communication: Dec 11, 2020.
14. Graves NM, et al. Rectal Administration of Antiepileptic Drugs in Children. Pediatr Neurol. 1987;3(6):321-326.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Albuterol (ProAir, Proventil, Ventolin)[1,9]	**Bronchospasm** Rescue dosing frequency for all inhaled forms can be as often as Q20 minutes PRN for up to 3 doses. Amount per initial dose is based on dosage form and weight as follows: Inhaler: 1-2 puffs Nebulized: <u>10-15 kg:</u> 1.25mg <u>2 years & >15kg:</u> 2.5mg Maximum: after rescue dosing, doses are not typically repeated more often than Q3 hours PRN; typically not more than 6 doses/day	Metered Dose Inhaler (MDI): 90mcg/ actuation Solution for nebulization: 0.021% (0.63mg/3ml), 0.042% (1.25mg/3ml), 0.083% (2.5mg/3ml), 0.5% (5mg/ml)	• 0.042% and 0.083% are the most commonly prescribed strengths in pediatrics • Young children may require a spacer and mask for the inhaler and a mask for nebulizing • Size of masks varies and is determined by the manufacturer • CNS stimulation, hyperactivity, and insomnia occur more often in children than adults • Syrup and tablet dosage forms are available but are not preferred due to lower efficacy and greater side effects	-
Albuterol-ipratropium (Duoneb, Combivent)[1,2,9]	**Bronchospasm** Rescue dosing frequency can be as often as Q20 minutes PRN for up to 3 doses. Amount per initial dose is based on age as follows: <u><12 years:</u> 1.5-3ml <u>≥12 years:</u> 3ml Maximum: after rescue dosing, not more than 4 doses/day	Solution for nebulization: 0.5mg ipratropium-2.5mg albuterol/3ml	• See comments for individual agents • The nebulized route is preferred in pediatrics; MDI use is uncommon	-
Atropine (Isopto)[9,16,17]	**Secretions** Initial: 1-2 drops PO/SL PRN or Q4H MDD: not established for this indication	Ophthalmic solution: 1% Note: most OPPC locations compound a flavored 1% oral solution	• Ophthalmic solution may be used orally / sublingually • May cause facial flushing	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Dexmedetomidine (Precedex)[2,3,4,5]	**Agitation / Restlessness / Delirium** Initial: 1-4mcg/kg IN Q2 hours PRN MDD: unknown, evidence to support 4 doses in 24 hours	Solution for injection: 100mcg/ml	• Administer using nasal atomizer and divide dose between nostrils • Intranasal onset of action is dose-dependent and typically 10-40 minutes, with peak effects observed in 90-105 minutes • Theoretical risk of hypotension, bradycardia, but not observed in case reports • Concentrated IV formulation should be utilized, not diluted IV bag or bottle (product not listed)	-
Furosemide (Lasix)[1,2,9]	**Edema** Initial (PO/SL): 0.5-2mg/kg Q6-24 hours (20-80mg/dose) Initial (IV/IM/SQ): 0.5-2mg/kg Q6-24H (20-40mg/dose) MDD (PO/SL/IV/IM/SQ): 6mg/kg/day (200mg/dose, 600mg/day)	Oral solution: 8mg/ml, 10mg/ml Solution for injection: 10mg/ml Tablet: 20mg, 40mg, 80mg	• If administering SL, dose should be held beneath the tongue for ~5 minutes without administration of drink or food • If initial dose not effective in producing diuresis, increase by 0.5-1mg/kg with next dose • Not recommended in oliguric patients	Y
Haloperidol (Haldol)[1,6,7,8,9,18]	**Agitation / Restlessness / Delirium** Initial (PO): <u>≥3 years old</u> 0.01-0.02mg/kg Q8-12 hours. Initial (IM/SQ): 0.006-0.012mg/kg Q8-12H For severe, acute agitation, may repeat dose again in 1-2 hours via any dosage route MDD (PO): 0.05mg/kg/dose or 2mg/dose Q6H, whichever is less MDD (IM/SQ): 0.1mg/kg/day divided Q4-8H or 5mg/day whichever is less	Oral solution: 2mg/ml Solution for injection: 5mg/ml Tablet: 0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg	• Reserve for patients who are not responsive to other agents because pediatric patients are at increased risk of adverse effects including dystonia • Doses for acute agitation are higher than those used for nausea and vomiting; these higher doses should only be administered short term • Lowers seizure threshold; use with caution in patients at risk for seizure • Depot form (decanoate) should not be used	Y

Pediatric Dosing & Comments for Additional Medications

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Hydroxyzine HCl (Atarax) Hydroxyzine pamoate (Vistaril)[1,2,9]	**Anxiety / Itching** Initial: <u>≤6 years old:</u> 0.5mg/kg or 12.5mg/ dose PO (whichever is less) BID-QID PRN <u>≥6 years old:</u> 0.5mg/kg or 25mg/dose PO (whichever is less) BID-QID PRN MDD: 100mg/dose or 200mg/day, whichever is less	Capsule: 25mg, 50mg, 100mg Oral syrup: 2mg/ml Tablet: 10mg, 25mg, 50mg	• Younger patients may require more frequent dosing (QID) compared to older children (BID) due to faster elimination • Either salt can be used for anxiety or itching, despite convention to use HCl for itching and pamoate for anxiety	Y
Ipratropium (Atrovent)[1,2,9]	**Bronchospasm** Rescue dosing frequency can be as often as Q20 minutes PRN for up to 3 doses. Amount per initial dose is based on age as follows: <u>≤12 years old:</u> 1.5-3ml <u>≥12 years old:</u> 3ml Maximum: after rescue dosing, not more than 4 doses/day	Solution for nebulization: 0.02%	• Ipratropium is an anticholinergic bronchodilator that can also decrease secretions • The nebulized route is preferred in pediatrics; MDI use is uncommon	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Levalbuterol (Xopenex)[1,2,9]	**Bronchospasm** Rescue dosing frequency for all inhaled forms can be as often as Q20 minutes PRN for up to 3 doses. Amount per initial dose is based on dosage form and age as follows: Inhaler: 1-2 puffs Nebulized: <u>≤4 years old:</u> 0.31-1.25mg <u>5-11 years old:</u> 0.31-0.63mg <u>≥12 years old:</u> 0.63-1.25mg Maximum (Inhaler): after rescue dosing, not more than 2 puffs Q4 hours Maximum (nebulized): after rescue dosing, not more than: <u>≤4 years old:</u> 1.25mg Q4 hours <u>5-11 years old:</u> 0.63mg Q6 hours <u>≥12 years old:</u> 1.25mg Q6 hours	Metered Dose Inhaler (MDI): 45mcg/ actuation Solution for nebulization: 0.31mg/3ml, 0.63mg/ml, 1.25mg/3ml, 1.25mg/0.5ml	• Duration of action is longer with nebulized solution (5-8 hours) than with MDI (3-6 hours) • Levalbuterol is the (R)-enantiomer of albuterol which is marketed to cause fewer side effects like tachycardia, though this is questionable • Guidelines recommend less frequent dosing for older children than children ≤4 years old • Counterintuitively, recommended doses for those ≤4 years old exceed those recommended for 5-11 year olds	-

Pediatric Dosing & Comments for Additional Medications

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Loperamide (Imodium)[1,2,9]	**Diarrhea** Initial: 2-5 years old & at least 13kg: 1mg PO initially, then 1mg following each loose stool 6-11 years old & least 21 kg: 2mg PO initially, then 1-2mg after each stool ≥12 years old: 4mg PO initially, then 2mg after each stool MDD: 2-5 years old & at least 13kg: 3mg/day 6-8 years old & at least 21kg): 4mg/day 9-11 years old & at least 27kg: 6mg/day ≥12 years old & at least 45kg: 16mg/day	Capsules: 2mg Oral solution: 1mg/7.5ml Tablets: 2mg	• Not recommended for treatment of infectious diarrhea • Generally intended for short term use, with exception for patient's with chronic intestinal disease • If patient's age and weight do not correspond, use the lower of the two dosing options	Y
Lorazepam (Ativan)[1,6,7,8,9]	**Agitation / Anxiety / Restlessness / Delirium** Initial (PO, SL, IV, IM, SQ): 0.02-0.05mg/kg (NTE 2mg/dose) Q6hr PRN *For severe, acute agitation, may repeat dose again in 1-2 hours via any dosage route.* MDD: 12mg/day; 0.1mg/kg/dose or 2mg/dose whichever is lower, 6 doses/day	Oral solution: 2mg/ml, 4mg/ml Solution for injection: 2mg/ml, 4mg/ml Tablet: 0.5mg, 1mg, 2mg	• Doses used for agitation, anxiety are lower than seizure but can be utilized more frequently • Onset of action is approximately 30 minutes when administered orally with peak affect at ~2 hours and approximate duration of 8 hours • For terminal restlessness, may administer repeated doses in closer intervals of every 1-2 hours if benefits outweigh risks	Y

Pediatric Dosing & Comments for Additional Medications

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Melatonin [9,14,15]	**Insomnia** Initial: <u>≤1 year old:</u> 0.5-1mg PO QHS <u>1-12 years old:</u> 1-2mg PO QHS <u>≥12 years old:</u> 2-3mg PO QHS MDD: 10mg/day (not well-established)	Various	• Administer within 1 hour of bedtime • Effectively treats sleep-onset insomnia, but not sleep maintenance insomnia • May administer an additional dose PRN for nighttime awakenings	variable
Olanzapine [1,2,9] (Zyprexa)	**Agitation / Restlessness / Delirium** Initial: <u>4-11 years old:</u> 0.1-0.14mg/kg QD or 2.5mg, whichever is less <u>≥12 years old:</u> 2.5mg PO QD MDD: 20mg QD in single or divided doses	Orally Disintegrating Tablet (ODT)*: 5mg, 10mg, 15mg, 20mg Tablet: 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg	• Dose must be rounded to closest 1.25mg increment due to tablet size • Limited data in patients 4-12 years old; use with caution • Dosing for agitation / restlessness / delirium is not well elucidated and has been extrapolated from recommended antiemetic doses • Risk of hyperprolactinemia is greater in adolescents than in adults • *ODTs can be cut, but the remaining part often needs to be discarded due to environmental exposure / humidity	Y*
Propranolol (Inderal, InnnoPran) [1,6]	**Anxiety / Restlessness** Initial: 0.5mg/kg/day PO divided BID-QID MDD: 4mg/kg/day divided TID-QID or 80mg/dose, whichever is less	Capsule (ER)*: 60mg, 80mg, 120mg, 160mg Oral solution: 4mg/ml, 8mg/ml Tablet: 10mg, 20mg, 40mg, 60mg, 80mg	• Give consistently with or without food • Not recommended in patient with asthma or those requiring bronchodilators • Use cautiously in patients at risk for hypoglycemia because symptoms can be masked • When possible, taper to discontinue and avoid abrupt discontinuation	Y/N*
Quetiapine (Seroquel) [9,20]	**Agitation / Restlessness / Delirium** Initial (IR): 0.4mg/kg (NTE 12.5mg/dose) QD-BID MDD: 0.78mg/kg/dose up to Q8H or 300mg/day, whichever is less	Tablet (IR): 25mg, 50mg, 100mg, 300mg, 400mg Tablet (ER)*: 50mg, 150mg, 200mg, 300mg, 400mg	• Doses used for delirium are significantly lower than those for schizophrenia and bipolar disorders • ER tablet should be administered without food or with a light meal; IR tablet can be administered without regard to food	Y/N*

Pediatric Dosing & Comments for Additional Medications

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Risperidone (Risperdal) [1,2,6, 9]	**Agitation / Restlessness / Delirium** Initial: 0.01mg/kg/day PO divided QD-BID (NTE 0.25mg/day) MDD: 4mg/day divided QD-QID	Oral Disintegrating Tablet (ODT)*: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg Oral solution: 1mg/ml Tablet: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg	• Oral solution should not be co-administered with liquids including tannin or pectinate (eg, coffee, cola, tea, apple juice) • Risk of hyperprolactinemia is greater in adolescents than in adults • *ODTs can be cut, but the remaining part often needs to be discarded due to environmental exposure / humidity	Y*
Sildenafil (Revatio)[1,9]	**Pulmonary arterial hypertension** Typical dosing range: <u><1 year old:</u> 0.25mg/kg Q6H OR 0.5mg/kg PO Q8H up to 2mg/kg/dose Q6-8H <u>≥1 year old:</u> 10-40mg PO TID	Oral suspension: 10mg/ml Tablet: 20mg	• Unlikely to be initiated in the hospice setting and will likely be a continuation of care from prior to hospice admission	Y
Simethicone (Gas-X, Mylicon)[1]	**Flatulence** Initial: <u><2 years old:</u> 20mg PO QD-QID PRN <u>2-12 years old:</u> 40mg PO QD-QID PRN <u>≥12 years old:</u> 125mg PO QD-QID PRN MDD: <u><2 years old:</u> 240mg/day <u>2-12 years old:</u> 480mg/day <u>≥12 years old:</u> 500mg/day	Capsules*: 125mg, 180mg, 250mg Chewable tablet: 80mg, 125mg Oral film: 40mg, 62.5mg Oral suspension: 20mg/0.3ml	• Medication is not absorbed and poses a low risk for toxicity	Y/N*
Sodium chloride (HyperSal, Hebusal, PulmoSal)[1,9]	**Respiratory secretions** Initial: 1 dose PRN or Q2H for 3 doses MDD: 4 doses/day	Solution for nebulization: 0.9%, 3%, 3.5%, 7%, 10%	• Optimal dose not well-defined • Patients should generally be started with NS product (0.9%) and progress toward hypertonic formulations if they have inadequate response • Typically ultra-concentrated products (7-10%) are reserved for patients with extremely thick secretions such as patients with cystic fibrosis • Highly concentrated products should be pretreated with bronchodilators to prevent bronchospasm.	-

Pediatric Dosing & Comments for Additional Medications

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Trazodone (Desyrel)[1,9]	**Insomnia** Initial: 1.5-3 years old: 12.5-25mg PO QHS 3-5 years old: 25-50mg PO QHS ≥5 years: 25-50mg PO QHS MDD: 1.5-3 years old: 100mg/day 3-5 years old: 150mg/day ≥5 years old: 200mg/day	Tablets: 50mg, 100mg, 150mg, 300mg	• Take consistently with or without food • Has serotonergic activity; use with caution in patients receiving one or more serotonergic agents • Rare reports of priapism in males	Y
Zolpidem (Ambien)[1,9]	**Insomnia** Initial (≥2 years old): 0.25mg/kg PO QHS MDD: 10mg/day, consider a maximum of 5mg/day for females based on adult data	Tablet (IR): 5mg 10mg Tablet (ER)*: 6.25mg, 12.5mg Tablet (SL): 1.75mg, 3.5mg	• Use sparingly; safety and efficacy has not been established in pediatric patients • Administered immediately prior to bedtime • Do not administer immediately after meals because onset will be delayed • Child should be allowed to sleep at least 8 hours after dosing • Can cause hallucinations, wandering, nighttime eating	Y/N*

References

1. Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; December 2020
2. Micromedex Solutions, Ann Arbor, Michigan: Truven Health Analytics; December 2020
3. Bartoletta KM, Collura CA, et al. Novel Use of Intranasal Dexmedetomidine for Neurologic Irritability in the Home Setting. Poster Presented at: American Academy of Hospice and Palliative Medicine Annual Assembly, Feb. 2021.
4. De Zen L, Del Rizzo I, et al. Home Use of Intranasal Dexmedetomidine in a Child with an Intractable Sleep Disorder. J Pediatr Pharmacol Ther. 2020; 25(4): 332-335.
5. De Zen L, Della Paolera S, et al. Home Intranasal Dexmedetomidine for Refractory Dystonia in Pediatric Palliative Care. J Pain Symtom Manage. 2020; 59(6):e3-e5.
6. Wusthoff CJ, Shellhaas RA, Licht DJ. Management of common neurologic symptoms in pediatric palliative care: seizures, agitation, and spasticity. Pediatric Clin North Am. 2007;54(5):709-733.
7. Rasmussen LA, Gregoire MC. Challenging neurological symptoms in paediatric palliative care: An approach to symptom evaluation and management in children with neurological impairment. Paediatr Child Health. 2015; 20(3): 159-1
8. Hauer J, Houtrow AJ. AAP Section on Hospice and Palliative Medicine, Council on Children with Disabilities. Pain Assessment and Treatment in Children with Significant Impairment of the Central Nervous System. Pediatrics. 2017;139(6):e20171002
9. Author opinion
10. Cozzi G, Lega S, et al. Intranasal Dexmedetomidine Sedation as Adjuvant Therapy in Acute Asthma Exacerbation with Marked Anxiety and Agitation. Ann Emerg Med. 2017;69:125-127.
11. American Psychological Association. "Anxiety". 2021. https://www.apa.org/topics/anxiety
12. Goldman A, Hain R, Liben S. Oxford Textbook of Palliative Care for Children. Oxford: Oxford University Press; 2012.
13. Schechter NL, Berde CB, Yaster M. Pain in infants, children, and adolescents. Philadelphia, PA. Lippincott Williams & Wilkins, 2003.
14. Janjua I, Goldman RD. Sleep-related melatonin use in healthy children. Can Fam Physician. 2016;62(4):315-316.
15. Cummings C, Canadian Paediatric Society, Community Paediatrics Committee. "Melatonin for the management of sleep disorders in children and adolescents" Practice Point. Posted: 2012, Reaffirmed: 2021
16. Rapoport A. Sublingual atropine drops for the treatment of pediatric sialorrhea. J Pain Symptom Manage. 2010; 40(5):783-8.
17. Saarnivaara L, Kautto UM, et al. Comparison of pharmacokinetic and pharmacodynamic parameters following oral and intramuscular atropine in children. Atropine overdose in two small children. Acta Anaesthesio Scand. 1985;29(5):529-36.
18. Zaprowska-Stachowiak I, Stachowiak-Szymczak K, et al. Haloperidol in palliative care: indications and risks. Biomedicine & Pharmacotherapy. 2020; 132: 110772
19. Zanaflex. [Package insert]. Ardsely, NY 10502: Acord Therapeutics Inc; 2013.
20. Capino AC, Thomas, AN, et al. Antipsychotic Use in the Prevention and Treatment of Intensive Care Unit Delirium in Pediatric Patients. J Pediatr Pharmacol Ther. 2020;25(2):81-95.

OnePoint®
PATIENT CARE

What one can do.®

Palliative Management of Diseases, Conditions, & Infections

Bowel Obstruction

DEFINITION

A blockage anywhere within the intestine that prevents the transit of stool, partially or completely.

CAUSES

- Conditions that cause narrowing of the intestinal lumen:
  - » Compression of the colon
  - » Tumors
  - » Adhesions
  - » Inflammation
  - » Hernias
- Conditions that impair the normal function of the intestines:
  - » Trauma
  - » Paralytic ileus
  - » Diabetic gastroparesis
  - » Mesenteric embolus/thrombus
  - » Hypokalemia

HOW TO RECOGNIZE SYMPTOM

- Symptoms vary by location of the obstruction:
  - » Obstructions higher in the GI tract often cause vomiting
  - » Obstruction in lower areas of the small intestine cause colicky pain, distension, and increased bowel sounds
  - » Obstruction of the large intestine typically cause abdominal pain/distension, vomiting or watery diarrhea

CLINICAL INSIGHTS

- Multidrug therapy using agents with differing mechanisms of action is often necessary to control symptoms
- If needed, pain and nausea/vomiting associated with bowel obstruction should be treated with opioids and antiemetics, respectively (see chapters on pain and nausea/vomiting)
- Because the oral route often becomes ineffective, non-oral routes such as SL/PR/parenteral are commonly employed for effective drug delivery
- Stimulant laxatives, such as sennosides and bisacodyl, are contraindicated and can worsen symptoms
- Classification of bowel obstruction as partial versus complete is often dynamic (ie, partial may become complete and vice versa)
- For either partial or complete obstruction:
  - » Dexamethasone may be used to reduce inflammation
  - » Octreotide can be used to decrease gastric secretions and improve symptoms
- For partial obstruction:
  - » Metoclopramide can improve motility if the bowel is functional
  - » Docusate may be beneficial to soften stools to ease its passage
- For complete obstruction:
  - » Anticholinergics may decrease bowel contractions and relieve pain

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MEDICATIONS USED FOR EITHER PARTIAL OR COMPLETE BOWEL OBSTRUCTION:				
Dexamethasone (Decadron)	Initial:4mg IM/IV/SQ QD-BID MDD: not established for this indication	Solution for injection: 4mg/ml, 10mg/ml	• May help reduce edema and inflammation around obstruction	-
Octreotide (Sandostatin)	Initial (bolus): 100mcg IV/ SQ BID-TID Initial (continuous infusion): 10-20mcg/hr IV/SQ/ hr MDD (bolus): 900mcg/day MDD (continuous infusion): 40mcg/hr	Solution for injection: 50mcg/ml,100mcg/ml, 200mcg/ml,500mcg/ml, 1,000mcg/ml	• May show benefit in patients where other therapies have shown to be ineffective • May require use in conjunction with other agents listed • Up to 90% of patients respond to doses of 600-800mcg/day • Expensive	-
MEDICATIONS USED FOR PARTIAL OBSTRUCTION ONLY:				
Docusate sodium (Colace)	Initial: 100mg PO BID MDD: 800mg/day	Capsule*: 50mg, 100mg, 250mg Oral solution: 50mg/5ml Tablet: 100mg	• Oral solution has a very poor taste and is only recommended if given via tube	Y/N*
Metoclopramide (Reglan)	Initial: 10mg IM/IV/SQ q6h MDD: 40mg/day	Solution for injection: 10mg/ml	• Discontinue if colic occurs • Useful for partial obstruction	Y
MEDICATIONS USED FOR COMPLETE OBSTRUCTION ONLY:				
Glycopyrrolate (Robinul)	Initial: 0.2-0.4mg IM/IV/SQ q8 hours MDD: 1.2mg/day	Solution for injection: 2mg/ml	• Doesn't cross the Blood Brain Barrier (BBB), therefore less likely to contribute to or cause delirium • PO/SL bioavailability is very low; not recommended for this indication	-
Hyoscyamine (Levsin, Anaspaz)	Initial (IM/IV/SQ): 0.25mg q6h PRN Initial (SL): 0.125-0.25mg SL q4-6h PRN MDD: 1.5mg/day	Solution for injection: 0.5mg/ml Oral solution: 0.125mg/ml Tablet (SL): 0.125mg	• Rapid onset and near completely bioavailable when given sublingually	Y
Scopolamine (Transderm-Scop)	Initial: 1.5mg TD patch topically q 72h MDD: 2 patches/3 days	Transdermal patch: 1.5mg	• Monitor for anticholinergic effects, may worsen delirium/ alter mental status • Expensive	-

References

- Bruera, E. et al. Textbook of Palliative Medicine, 2006, pp. 588-600.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 236-8.
- EPEC-O Education in Palliative and End-of-life Care for Oncology, Self-study module 3e: Bowel obstruction, accessed online Nov. 2015 at: http://www.cancer.gov/resources-for/hp/education/epeco/self-study/module-3/module-3e.pdf
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 725,851-7.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. 2010. pp. 99-102.

Atrial Fibrillation & Atrial Flutter

DEFINITIONS[1]

Arrhythmia is a disturbance of normal heart rhythm.

Atrial fibrillation (AFib), the most common arrhythmia, is an irregularly irregular heart rhythm in which the heart beats in no particular pattern, order, or interval. Disambiguation: unless otherwise specified, this monograph refers to non-valvular atrial fibrillation.

Atrial flutter (AFlu) is a fast and regular heart rhythm that occurs less frequently than AFib, but often coexists with (and may even cause) AFib.

ASSOCIATED SYMPTOMS[1]

- Palpitation: an awareness of the heartbeat potentially caused by a rapid heart rate, arrhythmia, or forceful cardiac contraction.
  - » Described as "skipped beats"; flipping sensation in the chest; fullness or pounding in throat, neck, or chest
- Additional symptoms may include anxiety, lightheadedness, syncope (rapid onset, short duration), chest discomfort, fatigue, and shortness of breath.
- Some patients are asymptomatic.

CLINICAL INSIGHTS

- AFib and AFlu often coexist and can even transform into each other.[2] The sequelae and approach to drug therapy of the two conditions are similar.

ANTICOAGULATION

- In the hospice setting, keeping symptoms suppressed with rate and/or rhythm control becomes more important than anticoagulation, which is non-palliative / does not improve symptoms.
  - » The decision to continue / discontinue anticoagulation in hospice patients should consider the risk of stroke vs. the risk of anticoagulant-induced bleeding.
  - » The $CHADS_2$ / CHA_2DS_2-VASc approximate stroke risk and bleeding risk assessments like HAS-BLED can be considered; however, neither has been validated in a hospice population.
- Novel oral anticoagulants (NOACs) are clinically superior to warfarin, particularly in patients with non-valvular AFib. Warfarin is associated with higher rates of stroke / embolism, mortality, and major bleeding.[4]
- Antiplatelets as alternatives to anticoagulants
  - » Despite reduced efficacy, hospice providers cite patient / family preference, bleeding concerns, and better alignment with hospice goals of care as reasons for substituting aspirin (ASA) for anticoagulants[5]; this practice may also represent attempts to compromise with those reluctant to discontinue all preventative therapy.
  - » ASA is inferior to anticoagulants for stroke prevention and has low clinical utility in patients with AFib/AFlu; it is not beneficial for stroke prevention in patients >75 years old, does not prevent severe strokes, and does not significantly reduce the risk for major bleeding.[3,4,5]
  - » Bleeding risk with dual antiplatelet therapy (DAPT) is similar to that with oral anticoagulants. As such, DAPT should not be substituted for anticoagulants in an effort to improve safety.[4]
  - » When continued stroke prophylaxis is consistent with the hospice plan of care, NOACs are preferred over antiplatelet regimens.[4]

RATE CONTROL

- Hospice clinicians likely encounter more patients receiving drug therapy for rate control than for rhythm control, since rate control reduces hospitalization risk to a greater extent and is better tolerated in elderly patients.[1,6,7]
  - » Palliative benefit: Chest discomfort, dizziness, and dyspnea improve with rate control.[8]
  - » Medications typically used for rate control include digoxin, beta-blockers, non-dihydropyridine calcium channel blockers, and amiodarone (also provides rhythm control).
- Digoxin is a renally cleared medication with a narrow therapeutic index; chronic toxicity is a significant concern, particularly in those with renal impairment, hypothyroidism, or concomitant amiodarone use.

- » Signs and symptoms of toxicity: visual disturbances (blurred vision, yellow vision, halos), arrhythmia, GI symptoms (nausea, vomiting, diarrhea, abdominal pain), delirium, and headache.[9]
  - ° Presence of these symptoms in patients taking digoxin should prompt suspicion of toxicity.
- » Consider deprescribing digoxin or obtaining laboratory values when toxicity is suspected, depending on goals of care.

RHYTHM CONTROL

- Antiarrhythmic drugs (AADs) used to maintain sinus rhythm include amiodarone, dronedarone, dofetilide, flecainide, propafenone, and sotalol.[3]
  - » Because amiodarone is the most effective AAD for preventing AFib recurrence, hospice clinicians are more likely to encounter its use than other AADs.[1,7]
  - » Sotalol has unique antiarrhythmic properties that other beta-blockers lack.[1]
- Optimal deprescribing strategies for AADs at end-of-life have not been defined. However, presence of drug contraindications, precautions, interactions, adverse effects and inability to appropriately monitor use weigh in favor of deprescribing (**Table 1**).
- Amiodarone's long half-life (mean: 40-55 days; up to 107 days) allows its effects to persist for weeks to months after stopping long-term therapy.[1,9,14] As such, it is a rational target for deprescribing in hospice patients, particularly those with a prognosis of days to weeks.
  - » Amiodarone can be restarted if prognosis improves or arrhythmia recurs. Arrhythmia control generally occurs rapidly once treatment resumes.[14]
- Many AADs can prolong the QTc interval, subsequently increasing the risk for developing torsades de pointes (a rare arrhythmia that can lead to sudden cardiac death). They should be used cautiously in combination with other medications known to prolong the QTc interval or alter the metabolism of QTc-prolonging agents. (Appendix: Medications that Prolong the QTc Interval).
  - » Dose modification, therapeutic substitution, and deprescribing should be considered in an effort to reduce the number of medications that prolong the QTc interval.

TABLE 1. FACTORS WEIGHING IN FAVOR OF DEPRESCRIBING ANTIARRHYTHMIC DRUGS

Medication	Contraindications / Precautions[8,10]	Adverse Effects[9,10] (All AADs have potential for proarrhythmia)	Geriatric Considerations[7,9,11,12]	Monitoring[9]	Additional Considerations[9,13]
Amiodarone	Lung disease, hepatic impairment, heart block, sick sinus syndrome, bradycardia-induced syncope, thyroid disorders	Many; more notable / common include bradycardia, prolonged QT interval, hypo- / hyperthyroidism, pulmonary toxicity, photosensitivity, blue-grey skin discoloration, visual disturbance / impairment, peripheral neuropathy, nausea	Increased sensitivity to cardiac effects, thyroid dysfunction Reduced renal / hepatic clearance may increase risk for toxicity	BP, HR, ECG, pulmonary function, chest X-Ray, thyroid function, LFTs, electrolytes, eye exam	Many drug interactions Additive effects when combined with QT-prolonging and HR-lowering drugs Discontinue if signs / symptom of hepatic injury, pulmonary toxicity (eg, dyspnea, nonproductive cough), dermatologic toxicity (eg, progressive skin rash with blisters, mucosal lesions), peripheral neuropathy (slow / incomplete resolution possible) Adverse effects / toxicity may occur or progress following discontinuation due to drug accumulation and long elimination half-life

TABLE 1. FACTORS WEIGHING IN FAVOR OF DEPRESCRIBING ANTIARRHYTHMIC DRUGS

Medication	Contraindications / Precautions[8,10]	Adverse Effects[9,10] (All AADs have potential for proarrhythmia)	Geriatric Considerations[7,9,11,12]	Monitoring[9]	Additional Considerations[9,13]
Beta-blockers (other than sotalol)	Symptomatic bradycardia, hypoglycemia, asthma / COPD, PVD, DM, myasthenia gravis, thyroid disorders, renal / hepatic impairment	Bradycardia, hypotension, fatigue, dizziness, bronchospasm, hyperkalemia, AV block	Bradycardia more common Increased bioavailability (propranolol)	BP, HR, blood glucose	Additive effects when combined with BP- / HR-lowering drugs May diminish effects of beta-agonist bronchodilators (more likely with non-selective agents) Abrupt discontinuation can lead to ischemic symptoms or cause acute hypertension / tachycardia; gradual discontinuation is generally recommended Do not prolong QT interval
Digoxin	Electrolyte imbalance (esp. hypokalemia / hypomagnesemia), thyroid disorders, renal impairment, low body weight, Wolff-Parkinson-White syndrome	Anxiety, confusion, depression, dizziness, delirium, hallucination, headache, gynecomastia, abdominal pain, nausea, vomiting, diarrhea, visual disturbances	Do not exceed 0.125 mg/day Reduced body mass and renal clearance increase risk for toxicity	HR, ECG, SCr, digoxin levels (if interacting drugs are started / discontinued, suspected toxicity, disease changes)	Narrow therapeutic index Consider deprescribing if toxicity is suspected or if challenging to maintain therapeutic levels Many drug interactions Additive effects when combined with HR-lowering drugs Does not prolong QT interval
Diltiazem	Renal / hepatic impairment, sick sinus syndrome, AV block, hypotension, pulmonary congestion, HF, fluid retention / edema	Peripheral edema, bradycardia, hypotension, dyspepsia, headache, dizziness, fatigue	Increased sensitivity to hypotensive effects Constipation more common	LFTs, renal function, BP, HR, ECG	Many drug interactions Additive effects when combined with BP- / HR-lowering drugs Does not prolong QT interval
Disopyramide	BPH / urinary retention, electrolyte imbalance, glaucoma, HF, heart block, renal / hepatic impairment, long QT syndrome, myasthenia gravis, Wolff-Parkinson-White syndrome	Hypotension, prolonged QT interval, nausea, vomiting, diarrhea, constipation, dry mouth, blurred vision, urinary hesitancy, syncope, dizziness, fatigue, myalgia	Reduced drug clearance Anticholinergic effects may be intolerable Potent negative intropic effects can induce HF	Renal / hepatic function, ECG, plasma levels (if intolerable anticholinergic effects)	Many drug interactions Additive effects when combined with QT-prolonging and anticholinergic drugs
Dofetilide	Renal / hepatic impairment, prolonged QT interval, heart block, sick sinus syndrome, electrolyte imbalance	Headache, chest pain, prolonged QT interval, dizziness, insomnia, nausea, diarrhea, respiratory tract infection, dyspnea	Reduced renal clearance	ECG (QTc), CrCl, K^+, Mg^+	Many drug interactions Additive effects when combined with QT-prolonging drugs
Dronedarone	Permanent AFib, HF, hepatic impairment, heart block, sick sinus syndrome, bradycardia	HF exacerbation, prolonged QT interval, renal / hepatic injury, pulmonary toxicity, rash, pruritus, diarrhea, nausea, weakness	Increased drug exposure	BP, HR, LFTs, electrolytes, ECG	Many drug interactions Do not combine with strong CYP3A4 inhibitors (eg, ketoconazole, cyclosporine, clarithromycin, nefazodone) Additive effects when combined with QT-prolonging and HR-lowering drugs Discontinue if new or worsening HF symptoms, signs / symptoms of hepatic injury or pulmonary toxicity

TABLE 1. FACTORS WEIGHING IN FAVOR OF DEPRESCRIBING ANTIARRHYTHMIC DRUGS

Medication	Contraindications / Precautions[8,10]	Adverse Effects[9,10] (All AADs have potential for proarrhythmia)	Geriatric Considerations[7,9,11,12]	Monitoring[9]	Additional Considerations[9,13]
Flecainide	Chronic AFib, HF, CAD, structural heart disease, pacemaker, electrolyte imbalance, concurrent use of ritonavir, renal / hepatic impairment	Dizziness, weakness, visual disturbance, dyspnea, palpitation, chest pain, prolonged QT interval, syncope, proarrhythmia, headache, fatigue, nausea, tremor	Reduced drug clearance Prolonged half-life	Renal / hepatic function, ECG, BP, HR, plasma levels (frequent if concomitant amiodarone, severe renal / hepatic impairment, or major changes in dietary milk consumption)	Narrow therapeutic index Many drug interactions Additive effects when combined with QT-prolonging and HR-lowering drugs May increase digoxin concentrations
Propafenone	HF, CAD, heart block, cardiac conduction abnormalities, bradycardia, hypotension, renal / hepatic impairment, asthma / COPD, electrolyte imbalance, myasthenia gravis	Taste disturbance, dizziness, fatigue, blurred vision, prolonged QT interval, angina, nausea, vomiting, constipation, headache, dyspnea	Reduced hepatic metabolism	Liver function	Many drug interactions Additive effects when combined with QT-prolonging and BP- / HR-lowering drugs
Quinidine	HF, renal / hepatic impairment, electrolyte imbalance, G6PD deficiency, heart block, dietary changes, anticholinergic intolerance, thrombocytopenia, myasthenia gravis	Palpitations, angina, prolonged QT interval, dizziness, fatigue, headache, diarrhea, upper GI distress	Reduced drug clearance Bioavailability and half-life increased	Renal / hepatic function, CBC	Narrow therapeutic index Many drug interactions Additive effects when combined with QT-prolonging and anticholinergic drugs Do not combine with levofloxacin or moxifloxacin
Sotalol	Renal impairment, prolonged QT interval, asthma, bradycardia, heart block, sick sinus syndrome, HF, electrolyte imbalance, DM, myasthenia gravis, PVD / Raynaud disease, thyroid disorder	Bradycardia, hypotension, prolonged QT interval, chest pain, palpitations, dizziness, fatigue, headache, dyspnea, nausea, vomiting, diarrhea, diaphoresis, visual disturbance	Reduced renal clearance Prolonged half-life Bradycardia more common	ECG, BP, HR, K^+, Mg^+, Renal function (CrCl)	Many drug interactions Additive effects when combined with QT-prolonging and HR-lowering drugs May diminish effects of beta-agonist bronchodilators Abrupt discontinuation can lead to ischemic symptoms or cause acute hypertension / tachycardia; gradual discontinuation is generally recommended
Verapamil	Hypotension, Wolff-Parkinson-White syndrome, Lown-Ganong-Levine syndrome, sick sinus syndrome, HF, LV dysfunction, fluid retention / edema, neuromuscular transmission disorders (eg, myasthenia gravis)	Headache, gingival hyperplasia, constipation, dizziness	Increased sensitivity to hypotensive effects Constipation more common	Liver function, BP, HR, ECG	Many drug interactions Additive effects when combined with BP- / HR-lowering drugs Does not prolong QT interval

Atrial Fibrillation & Atrial Flutter

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIARRHYTHMICS - CLASS IA[9]				
Disopyramide (Norpace, Norpace CR)	AFib Initial (IR): 100-200mg PO Q6 hours Initial (ER): 200-400mg PO Q12 hours MDD: not established; usually up to 800mg/day	Capsule: 100mg, 150mg Capsule (ER)*: 100mg, 150mg	**Antiarrhythmics - Class IA (Disopyramide & Quinidine)** • Rhythm control • Increase mortality; reserved for life-threatening arrhythmias • May precipitate or exacerbate heart failure • Major CYP3A4 substrates; many drug interactions • Prolong QT interval • Anticholinergic effects may be intolerable (esp. disopyramide) • Additive effects when combined with QT-prolonging and anticholinergic drugs **Disopyramide** • Avoid in BPH, urinary retention, glaucoma due to anticholinergic effects • Requires renal / hepatic dose adjustments **Quinidine** • Narrow therapeutic index • Toxicity should be suspected if GI side effects (diarrhea and upper GI distress are common) accompany symptoms of cinchonism (eg, hearing or visual disturbance, headache, flushing, mental status changes, vertigo)[15] • Caution in renal / hepatic impairment • Strong CYP2D6 inhibitor, P-glycoprotein inhibitor • Avoid grapefruit juice • 267mg quinidine gluconate = 200mg quinidine sulfate	Y/N*
Quinidine (Quinaglute, Quinidex)	AFib/AFlu Initial (IR): 200mg PO Q6 hours Initial (ER): 324mg PO Q8-12 hours MDD (IR/ER): not established	Tablet (sulfate): 200mg, 300mg Tablet (ER, gluconate)*: 324mg		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIARRHYTHMICS - CLASS IC[3,9]				
Flecainide (Tambocor)	AFib/AFlu Initial: 50mg PO Q12 hours MDD: 400mg/day	Tablet: 50mg, 100mg, 150mg	**Antiarrhythmics - Class IC (Flecainide & Propafenone)** • Rhythm control • Avoid in HF and ischemic or structural heart disease • Caution in renal / hepatic impairment • Many drug interactions • Prolong QT interval; additive effects when combined with other QT-prolonging drugs • Can be used for acute treatment of symptomatic AFib/AFlu (called "pill-in-the-pocket" approach); requires inpatient trial **Flecainide** • Narrow therapeutic index • Frequent monitoring required in severe renal / hepatic impairment • May cause dizziness, visual disturbances, dyspnea • Major CYP2D6 substrate **Propafenone** • Contraindicated if bradycardia, significant hypotension, asthma / severe COPD, electrolyte imbalance • May cause metallic taste, dizziness, fatigue, blurred vision, nausea, vomiting • Major CYP2D6 / CYP3A4 substrate, P-glycoprotein inhibitor • May increase warfarin concentrations • Bioavailability of ER capsule < IR tablet (ER 325mg BID ≈ IR 150mg TID)	Y
Propafenone (Rythmol)	AFib Initial (IR): 150mg PO Q8 hours Initial (ER): 225mg PO Q12 hours MDD (IR): 900mg/day MDD (ER): 850mg/day	Capsule (ER)*: 225mg, 325mg, 425mg Tablet: 150mg, 225mg, 300mg		Y/N*

Atrial Fibrillation & Atrial Flutter

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIARRHYTHMICS - CLASS III[8,9]				
Amiodarone (Cordarone, Pacerone)	AFib Initial: 100-200mg PO QD (following loading dose) MDD: 200mg/day (higher doses used during loading)	Tablet: 100mg, 200mg, 400mg	**Antiarrhythmics - Class III** • Rhythm control • Prolong QT interval; additive effects when combined with other QT-prolonging drugs • More drug interactions than most other AADs • Major CYP3A4 substrates **Amiodarone & Dofetilide** • Boxed warning: due to proarrhythmic effects, inpatient ECG monitoring recommended for initiation / re-initiation	Y
Dofetilide (Tikosyn)	AFib/AFlu Initial: 500mcg PO BID MDD: 1,000mcg/day	Capsule: 125mcg, 250mcg, 500mcg	**Amiodarone & Dronedarone** • May increase concentrations of warfarin or NOACs; reduced anticoagulant doses / discontinuation may be necessary • Avoid grapefruit juice	Y
Dronedarone (Multaq)	AFib Initial: 400mg PO BID MDD: 800mg/day	Tablet: 400mg	**Amiodarone** • Most effective AAD for maintaining sinus rhythm • Can be used for rate control if other medications unsuccessful or contraindicated • Caution in hepatic impairment • Take consistently with regard to meals • If GI upset occurs, give in divided doses BID to improve tolerability • Dyspnea and nonproductive cough are symptoms of pulmonary toxicity which is more common with prolonged use; deprescribing should be considered when this is suspected • Notable adverse effects include thyroid dysfunction, photosensitivity, blue-grey skin discoloration, visual disturbances • Long half-life; effects can persist for weeks to months after discontinuation • 100mg/day commonly used if elderly, low body mass • 100mg tablets expensive; if indicated, use ½ of 200mg tablet to reduce spend **Dofetilide:** • Renal dose adjustments required • Contraindicated if combined with cimetidine, clarithromycin, HCTZ, itraconazole, ketoconazole, megesterol, prochlorperazine, trimethoprim, verapamil **Dronedarone** • Structurally similar to amiodarone, but less organ toxicity • Contraindicated if permanent AFib, symptomatic HF, severe hepatic impairment • Contraindicated if combined with strong CYP3A4 inhibitors (eg, ketoconazole, cyclosporine, clarithromycin, nefazodone)	Y

Atrial Fibrillation & Atrial Flutter

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BETA(β)-BLOCKERS[3,9]				
Atenolol (Tenormin)	AFib/AFlu Initial: 25mg PO QD MDD: not established; usually up to 100mg/day	Tablet: 25mg, 50mg, 100mg	**Beta-Blockers** • Rate control • Caution if asthma / COPD; may diminish efficacy of β_2-agonist bronchodilators or cause bronchospasm (esp. non-selective agents) • Use caution in patients with diabetes; can cause hyperglycemia and/or mask hypoglycemia symptoms • May cause hypotension, bradycardia, fatigue • Avoid abrupt discontinuation; taper over 1-2 weeks when possible **Carvedilol, Nadolol, Pindolol, Propranolol, Sotalol, Timolol** • Non-selective beta-blockers; avoid if bronchospastic disease **Atenolol, Betaxolol, Bisoprolol, Nadolol, Pindolol, Sotalol, Timolol** • Caution in renal impairment; atenolol, betaxolol, nadolol, and sotalol require renal dose adjustments **Bisoprolol, Carvedilol, Metoprolol, Pindolol, Propranolol, Timolol** • Caution in hepatic impairment; carvedilol is contraindicated if severe impairment **Atenolol, Betaxolol, Bisoprolol, Metoprolol** • Preferred if asthma / COPD or concomitant bronchodilator use (β_1 selective agents) • Selectivity is lost at high doses **Carvedilol & Metoprolol** • Major CYP2D6 substrates • ER capsules can be opened and contents sprinkled on small amount of soft food *(Continued on next page)*	Y
Betaxolol (Kerlone)	AFib Initial: 20mg PO QD MDD: 20mg/day	Tablet: 10mg, 20mg		Y
Bisoprolol (Zebeta)	AFib/AFlu Initial: 2.5mg PO QD MDD: not established; usually up to 10mg/day	Tablet: 5mg, 10mg		Y
Carvedilol (Coreg)	AFib/AFlu Initial (IR): 3.125mg PO BID MDD: not established for this indication; usually up to 50mg/day	Capsule (ER): 10mg, 20mg, 40mg, 80mg Tablet: 3.125mg, 6.25mg, 12.5mg, 25mg		Y
Metoprolol (Kapspargo, Lopressor, Toprol XL)	AFib/AFlu Initial (IR): 25mg PO BID Initial (ER): 50mg PO QD MDD (IR): not established; usually up to 200mg/day MDD (ER): not established; usually up to 400mg/day	Capsule (ER): 25mg, 50mg, 100mg, 200mg Tablet: 25mg, 37.5mg, 50mg, 75mg, 100mg Tablet (ER)*: 25mg, 50mg, 100mg, 200mg		Y/N*
Nadolol (Corgard)	AFib Initial: 10mg PO QD MDD: not established; usually up to 240mg/day	Tablet: 20mg, 40mg, 80mg		Y
Pindolol (Visken)	AFib Initial: 5mg PO BID MDD: 30mg/day	Tablet: 5mg, 10mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BETA(β)-BLOCKERS (CONTINUED)[3,9]				
Propranolol (Inderal)	AFib/AFlu Initial (IR): 10mg PO TID MDD: not established; usually up to 160mg/day in 3 to 4 divided doses	Capsule (ER)*: 60mg, 80mg, 120mg, 160mg Oral solution: 20mg/5mL, 40mg/5mL Tablet: 10mg, 20mg, 40mg, 60mg, 80mg	**Carvedilol** • Vasodilating properties; if symptomatic hypotension occurs, consider switching to an alternative agent • Administer with food to slow absorption, prevent orthostatic hypotension **Pindolol** • Minimal effects on resting heart rate compared to other beta-blockers (intrinsic sympathomimetic activity) • Edema is a common adverse effect **Propranolol** • IR tablets should be taken on an empty stomach • Bioavailability approximately doubled in elderly patients; more conservative doses are reasonable **Sotalol** • Provides rate and rhythm control • Non-selective beta-blocker with antiarrhythmic effects; not interchangeable with other beta-blockers • Boxed warning: QT prolongation and ventricular arrhythmia; inpatient ECG and CrCl monitoring recommended for initiation / dose increases • Contraindicated if CrCl <40ml/min	Y/N*
Sotalol (Betapace, Betapace AF, Sorine, Sotylize)	AFib/AFlu Initial: 80mg PO BID MDD: 320mg/day	Oral solution: 5mg/ml Tablet: 80mg, 120mg, 160mg, 240mg		Y
Timolol (Blocadren)	AFib Initial: 10mg PO BID MDD: 60mg/day	Tablet: 5mg, 10mg, 20mg		Y

Atrial Fibrillation & Atrial Flutter

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CALCIUM CHANNEL BLOCKERS (CCBs) - NON-DIHYDROPYRIDINE (NON-DHP)[9]				
Diltiazem (Cardizem, Cartia XT, Taztia XT, Tiazac)	AFib/AFlu Initial (IR): 30mg PO QID Initial (ER, 12-hr): 60mg PO BID Initial (ER, 24-hr): 120mg PO QD MDD: not established; usually up to 480mg/day	Capsule (ER, 12-hr)*: 60mg, 90mg, 120mg Capsule (ER, 24-hr)*: 120mg, 180mg, 240mg, 300mg, 360mg, 420mg Tablet: 30mg, 60mg, 90mg, 120mg Tablet (ER, 24-hr)*: 120mg, 180mg, 240mg, 300mg, 360mg, 420mg	**Non-dihydropyridine CCBs** • Rate control • Contraindicated if hypotensive • Avoid in HF • Caution in hepatic impairment; verapamil requires dose adjustments • Caution in renal impairment • Headache is a common adverse effect • Dose-dependent constipation is common (esp. verapamil) • Additive effects when combined with BP- / HR-lowering drugs • Major CYP3A4 substrates, moderate CYP3A4 inhibitors; many drug interactions • Grapefruit juice may increase drug levels **Diltiazem** • IR tablets dosed TID-QID • Dose-dependent peripheral edema is common • *Most ER formulations should not be crushed or opened (Taztia XT and Tiazac are exceptions) **Verapamil** • Associated with more hypotension than diltiazem • ER formulations can be given QD or BID • ER capsules can be opened and contents sprinkled on small amount of soft food • Caution if combined with beta-blockers due to risk for bradycardia and heart block • Limit grapefruit juice; may increase drug concentrations • P-glycoprotein inhibitor • Can produce false-positive for presence of methadone in urine	Y/N*
Verapamil (Calan, Verelan)	AFib/AFlu Initial (IR): 40mg PO TID-QID Initial (ER): 120-180mg PO QD MDD: 480mg/day	Capsule (ER) 120mg, 180mg, 240mg, 360mg Tablet: 40mg, 80mg, 120mg Tablet (ER)*: 120mg, 180mg, 240mg		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CARDIAC GLYCOSIDE[9]				
Digoxin (Digitek, Lanoxin)	AFib/AFlu Initial: 0.125mg PO QD MDD: 0.25mg/day; doses >0.125mg/day increase risk of toxicity and adverse effects in elderly patients	Oral solution: 0.05mg/ml Tablet: 0.0625mg, 0.125mg, 0.25mg	• Rate control • Narrow therapeutic index • Drug toxicity is a common cause of ED visits, especially if female or >85 years old • Doses as low as 0.125mg QOD should be considered if elderly, low body mass, or reduced renal clearance to avoid toxicity • Signs / symptoms of toxicity include visual disturbances (blurred vision, yellow vision, halos), arrhythmia, GI symptoms (nausea, vomiting, diarrhea, abdominal pain), delirium, and headache • Additive effects when combined with other rate-lowering drugs • 0.0625mg tablets expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICOAGULANTS – NOVEL ORAL ANTICOAGULANTS (NOACs)[9,16]				
Apixaban (Eliquis)	Initial: 2.5mg PO BID if any two of the following: • ≥80 years old • weight ≤60 kg • SCr ≥1.5 mg/dl Otherwise, 5mg BID MDD: same as initial dosing	Tablet: 2.5mg, 5mg	**Novel oral anticoagulants** • Not palliative; use is solely preventative unless used to treat active DVT/PE • Significant advantages for use in terminally ill patients include fewer drug interactions and a lack of required blood monitoring or dietary limitations • Lower rates of stroke / embolism, mortality, and major bleeding compared to warfarin[4] • Generally, ASA is not recommended as a substitute for anticoagulation due to inferior efficacy, however it may be viewed as an acceptable compromise for patients reluctant to discontinue all preventative therapy[4] • Use cautiously in patients with increased risk for bleeding / falls or who take other medications associated with bleeding (eg, NSAIDs, antiplatelets) • Hold doses or deprescribe if active bleeding • Require renal dose adjustments • Avoid all except apixaban if CrCl <15ml/min • Avoid all except dabigatran in severe hepatic impairment • Major P-glycoprotein substrates (except rivaroxaban) **Apixaban & Rivaroxaban** • Major CYP3A4 substrates; many drug interactions **Dabigatran & Rivaroxaban** • Not recommended in patients ≥75 years old due to increased risk for GI bleeding **Edoxaban & Rivaroxaban** • Avoid if moderate to severe hepatic impairment *(Continued on next page)*	Y
Dabigatran (Pradaxa)	Initial: 110-150mg PO BID Consider using reduced dose (110mg BID) if increased bleeding risk MDD: same as initial dosing	Capsule: 75mg, 110mg, 150mg		N*
Edoxaban (Savaysa)	Initial: 30-60mg PO QD Consider using reduced dose (30mg QD) if ≥65 years old and any one of the following: • weight ≤60 kg • CrCl ≤50 • taking potent P-glycoprotein inhibitor MDD: same as initial dosing	Tablet: 15mg, 30mg, 60mg		Y
Rivaroxaban (Xarelto)	Initial: 15-20mg PO QD with evening meal Lower dose (ie, 15mg) indicated when combined with antiplatelets post-PCI with stent placement MDD: same as initial dosing	Tablet: 2.5mg, 10mg, 15mg, 20mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICOAGULANTS – NOVEL ORAL ANTICOAGULANTS (NOACs)[9,16] (CONTINUED)				
			Apixaban • Preferred NOAC if CrCl <15ml/min; less dependent on renal clearance • If 2.5mg dose indicated, consider using ½ of 5mg tablet to reduce spend **Dabigatran** • *Swallow capsules whole; removing capsule shell leads to significant increase in absorption and risk for serious adverse effects, including fatal bleeding • Must be stored in manufacturer's container / package to protect from moisture; capsules dispensed in bottle should be used within 4 months of opening **Edoxaban** • Avoid if CrCl >95ml/min (reduced efficacy) **Rivaroxaban** • Administer doses ≥15mg with food to ensure adequate bioavailability • Avoid concomitant use with drugs that are strong CYP3A4 / P-glycoprotein inhibitors (eg, ketoconazole) or inducers (eg, carbamazepine, phenytoin, rifampin)	

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTICOAGULANTS - VITAMIN K ANTAGONIST[9,16]				
Warfarin (Coumadin, Jantoven)	Initial: individualized dosing protocols exist; usually 2.5-5mg PO QD Pharmacogenomic-guided dosing algorithms have been published and can be used when genotype results are available MDD: individualized	Tablet: 1mg, 2mg, 2.5mg, 3mg, 4mg, 5mg, 6mg, 7.5mg, 10mg	• Not palliative; use is solely preventative unless used to treat active DVT/PE • Clinically inferior to NOACs, which are associated with lower rates of stroke / embolism, mortality, and major bleeding [4] • In the hospice setting, drug regimens change frequently and dietary intake is often inconsistent, making warfarin use problematic due to many drug and food interactions • PT/INR monitoring required (at least monthly, if stable INR); target INR = 2 to 3 for thromboprophylaxis in AFib/AFlu • Even with frequent therapeutic monitoring, hospice patients are often out of range [17] • Use cautiously in patients with increased risk for bleeding / falls or who take other medications associated with bleeding (eg, NSAIDs, antiplatelets) • Hold doses or deprescribe if active bleeding • Caution in renal / hepatic impairment • If GFR <30, warfarin may be preferred over NOACs due to more widespread clinical experience • Only anticoagulant indicated for treatment of valvular AFib • Generally, ASA is not recommended as a substitute for anticoagulation due to inferior efficacy, however it may be viewed as an acceptable compromise for patients reluctant to discontinue all preventative therapy[4]	Y

References

1. Zipes DP, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 11th ed. Philadelphia, PA: Elsevier; 2019.
2. Manolis AS. Contemporary diagnosis and management of atrial flutter: a continuum of atrial fibrillation and vice versa? Cardiol Rev. 2017 Nov/Dec;25(6):289-297.
3. January CT, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol. 2014;64:e1–e76.
4. Manning WJ, et al. Atrial fibrillation: Anticoagulant therapy to prevent thromboembolism. UpToDate (Lit review current through May 2021, accessed June 2021).
5. Kowalewska CA, et al. Prevalence and clinical intentions of antithrombotic therapy on discharge to hospice care. Journal of Palliative Medicine. 2017;20(11):1225-1230
6. Chatterjee S, et al. Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. Pacing Clin Electrophysiol. 2013;36:122–133.
7. Ehrlich C, et al. Updates in antiarrhythmic therapy for atrial fibrillation in geriatric patients. The Consultant Pharmacist. 2015;30(2): 82-91.
8. Reiffel JA. Ten pearls for the use of antiarrhythmic drugs for atrial fibrillation. American College of Cardiology. Published August 17, 2012. Accessed July 29, 2020. https://www.acc.org/latest-in-cardiology/articles/2014/07/18/15/12/ten-pearls-for-the-use-of-antiarrhythmic-drugs-for-atrial-fibrillation.
9. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.
10. Podrid PJ. Major side effects of beta-blockers. UpToDate (Lit review current through Dec 2020, accessed Dec 2020).
11. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society. 2019;67(4):674–694.
12. Gallagher P, et al. STOPP (Screening Tool of Older Persons Prescriptions) and START (Screening Tool to Alert Doctors to Right Treatment): consensus validation. International Journal of Clinical Pharmacology and Therapeutics. 2008;46(2):72–83.
13. Giardina E, et al. Amiodarone: Adverse effects, potential toxicities, and approach to monitoring. UpToDate (Lit review current through Dec 2020, accessed Dec 2020).
14. Lexicomp Online, AHFS DI – Amiodarone. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.
15. Lexicomp Online, Lexi-Tox – Quinidine. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.
16. January CT, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/ARS guideline for the management of patients with atrial fibrillation. Circulation. 2019;140:e125-e151.
17. Hill RR, et al. A descriptive evaluation of warfarin use in patients receiving hospice or palliative care services. J Thromb Thrombolysis. 2009;27:334–339

Heart Failure

DEFINITIONS[1]

Heart failure (HF) is a clinical syndrome caused by the inability of the heart to pump sufficient blood to meet the metabolic needs of the body. Heart failure can result from any disorder that reduces ventricular filling (diastolic dysfunction) and/or myocardial contractility (systolic dysfunction). Patients generally experience periods of relative stability with periodic exacerbations.

- **HFrEF:** HF with reduced ejection fraction (EF) (formerly, left-sided or systolic HF); EF ≤40%
- **HFpEF:** HF with preserved EF (formerly, right-sided or diastolic HF); EF >50%
- **HFmrEF:** HF with midrange EF; EF 41-49%

Decompensated heart failure describes an acute worsening of heart failure symptoms, often related to fluid overload, that causes serious respiratory distress and typically requires non-oral medications to stabilize symptoms.

ASSOCIATED SYMPTOMS[1,2]

- Dyspnea, orthopnea, cough, edema, fatigue / activity intolerance, cool or mottled extremities, loss of appetite or early satiety, weight gain (fluid), weight loss (cardiac cachexia), depression, anxiety, insomnia, pain

CLINICAL INSIGHTS

- Treatment is guided by heart failure type (HFrEF or HFpEF), severity (ie, NYHA functional classification), and comorbidities.
- Diuretics are used to relieve pulmonary congestion and edema and are a mainstay of treatment for both HFrEF and HFpEF.[2]
  - » Oral diuretics are ineffective during episodes of decompensated HF as a result of increased gut wall edema and reduced GI perfusion and motility. In these cases, non-oral routes (eg, IV/SQ/IM; possibly SL) are preferred due to improved bioavailability.[3,4] (**Figure 1**)
  - » Diuretic response is governed by a threshold type dose-response and diuresis will not occur until that threshold is reached. If a patient does not respond to a starting dose, increased doses are likely to be more effective than more frequent administration (eg, if unresponsive to 20mg dose, increase dose to 40mg instead of giving 20mg BID).[5,6]
  - » If furosemide doses ≥80mg BID are needed, consider rotation to an alternative loop diuretic or adding a thiazide diuretic (eg, metolazone).[7]
- Opioids may be necessary to treat refractory dyspnea.
- Oral medications that improve heart failure symptoms and quality of life should be continued in the hospice setting for as long as they are tolerated and the patient is still able to swallow them.[7] (**Table 1**)
- Some medications cause fluid retention, worsen underlying cardiac dysfunction, and precipitate HF exacerbations; their use should be limited or avoided altogether.[1,2] (**Table 2**)
  - » Systemic NSAIDs are the most common cause of drug-induced heart failure exacerbations and should be avoided because they cause sodium and water retention and can reduce the efficacy of diuretics and angiotensin system blockers.[2]

FIGURE 1: NON-ORAL LOOP DIURETIC ADMINISTRATION IS PREFERRED DURING HF EXACERBATIONS[3,4]

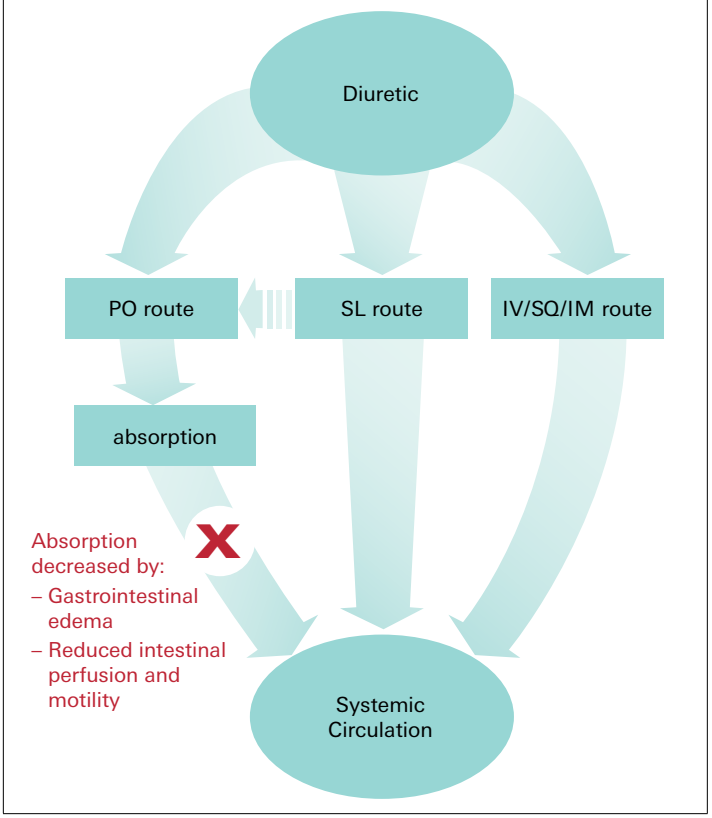


TABLE 1: PALLIATIVE HEART FAILURE MEDICATIONS [2,8]

Medication/Medication Class (evidence-based agents)	Improves symptoms, functional class, or exercise capacity	
	HFrEF	HFpEF
Aldosterone antagonists (spironolactone, eplerenone)	X	X
Angiotensin-converting enzyme inhibitors (ACEIs) (enalapril, captopril, ramipril, trandolapril, lisinopril)	X	X
Angiotensin-receptor blockers (ARBs) (candesartan, valsartan, losartan)	X	
Angiotensin receptor-neprilysin inhibitors (ARNI) (sacubitril/valsartan)	X	
Beta-blockers (metoprolol succinate, carvedilol, bisoprolol)	X	
Diuretics (furosemide, torsemide, bumetanide, metolazone)	X	X
I_f channel inhibitor (ivabradine)	X	
Inotropes (intravenous) (milrinone, dobutamine)	X	
Inotropes (oral) (digoxin)	X	
SGLT-2 inhibitors (dapagliflozin, empagliflozin)	X	
Vasodilators (isosorbide dinitrate + hydralazine)	X	

HFrEF

- Guideline-directed therapy usually consists of a combination of an angiotensin system blocker (ACEI, ARB, or ARNI), select beta-blocker, diuretic, spironolactone +/- add-on or alternate agents.
  - » HFmrEF: no specific guidelines exist; managed similarly to HFrEF[13]
- Multiple medications improve symptoms including fatigue, dyspnea, and exercise capacity.[2] (**Table 1**)
- Guidelines recommend that medications are titrated to a target dose (usually maximum indicated dose), as tolerated.
  - » If target doses are exceeded, dose reduction is reasonable since higher doses are not beneficial.[7]
  - » Previously tolerated doses may become intolerable as disease progresses; periodically monitor for symptomatic hypotension or bradycardia and reduce doses, if necessary.
  - » Do not reduce doses or deprescribe for mild hypotension or bradycardia that is well-tolerated by the patient.[14]
- Use of more than one angiotensin system blocker is not recommended.
- Calcium channel blockers (CCBs) should generally be avoided because they do not improve functional status or improve mortality.[15]
  - » However, in patients requiring treatment for hypertension and/or angina, amlodipine and felodipine have been safely used despite their propensity to cause edema.[15,16]
- Ivabradine and digoxin are secondary or add-on agents for patients who remain symptomatic despite treatment with or who cannot tolerate the combination of a diuretic, angiotensin system blocker, and beta-blocker.[17]
- Hydralazine plus isosorbide dinitrate may be preferred for certain patients:
  - » Particularly beneficial in African American patients[2]
  - » Add-on therapy if symptoms persist despite optimal treatment with other agents[17]
  - » Those with renal impairment or hyperkalemia and unable to tolerate angiotensin system blockers[2]
- IV inotropes can be considered for hemodynamically unstable patients with refractory HFrEF who remain symptomatic despite conventional therapy. (See Intravenous Inotrope section)

NEWER AGENTS

- Sacubitril/valsartan
  - » Sacubitril/valsartan is not well studied in patients with NYHA class IV HF. The PARADIGM-HF study demonstrated statistically significant benefit in patients with less severe HF.[18]
  - » The LIFE trial concluded that the combination is no better than valsartan in patients with severe HFrEF and is more likely to cause hypotension and hyperkalemia.[19]
  - » Considering the results of the LIFE trial and the capitated reimbursement received by hospices, it is preferable to substitute valsartan in place of sacubitril/valsartan.
- Originally used for the treatment of type 2 diabetes, certain SGLT-2 inhibitors (dapagliflozin and empagliflozin) have demonstrated improvements in survival time and reduced hospitalizations for patients with HFrEF. Both improve symptoms, function, and quality of life (dapagliflozin; NNT=10).[8,20,21]
  - » Like sacubitril/valsartan, this medication class is not well-studied in patients with NYHA class IV HF.[22]
  - » Deprescribing is recommended for patients with reduced oral intake, fluid loss, or who are hypotensive / volume-depleted.[9]

HFpEF

- Compared to HFrEF, there is less robust clinical evidence to guide treatment in HFpEF. Therapy is generally aimed at managing hypertension, arrhythmia (esp. tachyarrhythmia), CAD, pulmonary congestion, and peripheral edema.
- Aldosterone antagonists (usually spironolactone) are the only medications known to improve both symptoms and quality of life.[2]
- Small studies indicate that verapamil may improve symptoms.[2]

TABLE 2: DRUGS ASSOCIATED WITH HEART FAILURE SYMPTOMS AND EXACERBATIONS[9-11]

Drug / Class	Mechanism / Outcome
• Antiarrhythmics (flecainide, disopyramide, dronedarone) • Carbamazepine • Itraconazole • Ketamine* • Non-dihydropyridine CCBs (verapamil, diltiazem) • Propofol • Tricyclic antidepressants	Negative inotropic effects (reduced heart contractility)
• Alpha$_1$ blockers • CCBs except verapamil; (Dihydropyridines >> diltiazem) • Corticosteroids (when needed, use lowest effective dose; dexamethasone preferred)[2] • Dopamine agonists • Gabapentinoids (higher incidence with pregabalin) • Hydralazine • Lithium • NSAIDs • Sodium-containing drugs (eg, magnesium citrate, sodium phosphates) • Thiazolidinediones (Black Box Warning)	Volume overload / edema by various mechanisms
• Clozapine • Hydroxychloroquine • Lithium • Psychostimulants*	Cause increased cardiac strain / dysfunction, worsening HF symptoms
• Metformin	Both HF and metformin increase risk for lactic acidosis (LA), which is particularly concerning if concomitant renal / liver / pulmonary disease. LA and HF have some overlapping symptoms (eg, fatigue, dyspnea, reduced appetite)
• DPP-4 Inhibitors ('-gliptins')	Unknown mechanism; studies have shown increased rates of HF and HF complications

*Some practitioners argue that these risks are overstated and rapid benefits in treating depression at the end of life outweigh the risks.[12]

INTRAVENOUS (IV) INOTROPES

- Inotropes are medications that increase the force of heart muscle contraction.
- IV inotropes can be used as a palliative intervention for patients with refractory HFrEF, but there is little evidence to support use in HFpEF.[23]
- Benefits include palliation of HF symptoms (dyspnea, nausea, fatigue, edema, pain) and facilitation of end-of-life goals including wishes to die at home, reduced hospitalizations, and increased quality of life.[2,11,24-25]
- Administration requires central catheter placement and therapy is typically initiated prior to hospice enrollment.[26]
- Dobutamine and milrinone are the IV inotropes most commonly used for palliation of HF symptoms in the outpatient setting.[2] Both improve cardiac output and diuresis without exacerbating systemic hypotension.[27]
  - » There is no consensus regarding superiority of one agent over the other.
  - » Milrinone has a longer half-life and duration of effect; patients with renal insufficiency may be more susceptible to its adverse effects.[28]
  - » Use lowest effective dose to minimize proarrhythmic effects.[23]
  - » When used at doses typically administered in palliative care (see drug table), dobutamine tends to cost marginally less than milrinone. With higher doses, milrinone can cost twice as much as dobutamine.[23,29]
- Cost is a barrier to use in the hospice setting.
  - » Aside from direct drug costs, the costs of IV compounding, supplies, personnel / regular nursing visits should also be considered.[23,28]
- Patients otherwise eligible for hospice care may have difficulty finding a program willing to admit them if receiving continuous inotropic support due to cost, program philosophy or unfamiliarity; this could lead to delayed hospice election.[24]
- Hospices who admit inotrope-dependent patients should anticipate that some will require continued inotropic support and prepare to manage their care accordingly.
- Due to the risk for arrhythmia associated with IV inotropes and subsequent implanted cardioverter-defibrillator (ICD) shocks, hospice providers should have ongoing discussions about ICD status.[23]
  - » ICDs can be temporarily deactivated by hospice personnel to prevent painful shocks.[30]
- Complications with ongoing treatment should prompt a revisitation of end-of-life goals and weaning / withdrawing therapy should be considered.[23]
  - » Thrombosis, central line infection, worsening HF symptoms, patient / caregiver burden[23]
  - » Responsiveness may decrease over time (tachyphylaxis); this is less commonly observed with milrinone.[11,23]
- Inotrope weaning / withdrawal
  - » A published weaning protocol (**Figure 2**) demonstrated that patients can be kept comfortable with gradual inotrope tapering and discontinuation within one day.[28]
    - ° Significant clinical deterioration following attempts to wean or withdraw IV inotropes is a compelling indication to continue therapy.[23]
  - » In-home weaning is possible, but continuous home care should be considered due to the potential for severe symptoms to arise. General inpatient care may be preferred due to staff level of comfort / familiarity with aggressive symptom management.[28]
  - » Opioids, benzodiazepines, antiemetics, and diuretics can be used to manage associated symptoms. Non–pharmacologic interventions, including the use of fans and supplemental oxygen for hypoxic patients may also be considered.[28]
  - » Renal insufficiency, which is common in heart failure patients, prolongs the half-life of milrinone. Therefore, patients can present with worsening symptoms hours to days after weaning.[28]
  - » Patients who are hypotensive at baseline may die more quickly following withdrawal, while others may live for hours to months after inotrope discontinuation.[23]

FIGURE 2: EXAMPLE OF A WEANING PROTOCOL FOR IV DOBUTAMINE AND MILRINONE (FROM GRONINGER, ET AL.)[28]

Step 1	Document current dose (mcg/kg/min) and dosing weight (kg)	
Step 2	Evaluate for symptoms of advanced heart failure and document the following: • Dyspnea (none, mild, moderate, severe) • Respiratory rate • Anxiety / restlessness (none, mild, moderate, severe) • Pain (scale of 0-10, or other validated pain scale)	
Step 3	• Palliate symptoms (with opioids, benzodiazepines, oxygen, etc.) without weaning until patient is comfortable. • Dyspnea and anxiety / restlessness should be none or mild. Respiratory rate should be treated to < 20 breaths per minute. • Diuretics may be needed to manage fluid retention or dyspnea. IV/SQ administration with rapid dose escalation may be necessary and doses may be administered Q2 hours PRN. Diuretics should not be held for low blood pressure if symptomatic volume overload is present.	
Step 4	**Dobutamine**	**Milrinone**
	Decrease dose by 1mcg/kg/min.	Decrease dose by 0.125mcg/kg/min.
Step 5	Within 15 minutes of dose reduction, evaluate closely for symptoms of worsening HF / dyspnea.	Within one hour of dose reduction, evaluate closely for symptoms of worsening HF / dyspnea.
Step 6	If symptoms of worsening HF, palliate until patient is comfortable (Step 3).	If symptoms of worsening HF, palliate until patient is comfortable (Step 3).
Step 7	If patient is comfortable one hour after initial wean, dose can be decreased by an additional 1mcg/kg/min.	If patient is comfortable four hours after initial wean, dose can be decreased by an additional 0.125mcg/kg/min.
Step 8	Dobutamine can be weaned by 1mcg/kg/min as rapidly as every one hour, if the patient is comfortable, until the infusion is completely discontinued. For most patients, this protocol facilitates discontinuation, provided appropriate expertise in symptom management.	Milrinone can be weaned by 0.125mcg/kg/min as rapidly as every four hours, if the patient is comfortable, until the infusion is completely discontinued. For most patients, this protocol facilitates discontinuation, provided appropriate expertise in symptom management.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs)[9]				
Captopril (Capoten)	Initial: 6.25mg PO TID MDD: 150mg/day	Tablet: 12.5mg, 25mg, 50mg, 100mg	**ACE-Inhibitors** • Do not combine with ARBs, aliskiren, or take within 36 hours of sacubitril/valsartan • Angioedema involving the head, neck, or intestine can occur at any time during treatment and should prompt discontinuation • A dry, hacking, nonproductive cough is the most common adverse effect; it generally resolves within 1-4 weeks of discontinuation. Onset is variable; can occur up to 6 months after starting therapy. • Hyperkalemia risk increased in CKD or if taking potassium or potassium-sparing drugs • May cause symptomatic hypotension with or without syncope • Avoid if ascites due to cirrhosis or refractory ascites • Renal function may decline when initiating therapy; once therapy is established, renal dose adjustments may be required • Oral solutions are expensive	Y
Enalapril (Vasotec)	Initial: 2.5mg PO BID MDD: 40mg/day	Oral solution: 1mg/ml Tablet: 2.5mg, 5mg, 10mg, 20mg		Y
Fosinopril (Monopril)	Initial: 10mg PO QD MDD: 40mg/day	Tablet: 10mg, 20mg, 40mg		Y
Lisinopril (Zestril, Prinivil)	Initial: 2.5-5mg PO QD MDD: 40mg/day	Oral solution: 1mg/ml Tablet: 2.5mg, 5mg, 10mg, 20mg, 30mg, 40mg		Y
Perindopril (Aceon)	Initial: 2mg PO QD MDD: 16mg/day	Tablet: 2mg, 4mg, 8mg		Y
Quinapril (Accupril)	Initial: 5mg PO BID MDD: 40mg/day	Tablet: 5mg, 10mg, 20mg, 40mg		Y
Ramipril (Altace)	Initial: 1.25-2.5mg PO QD MDD: 10mg/day	Capsule: 1.25mg, 2.5mg, 5mg, 10mg		Y
Trandolapril (Mavik)	Initial: 1mg PO QD MDD: 4mg/day	Tablet: 1mg, 2mg, 4mg		Y
ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)[9]				
Candesartan (Atacand)	Initial: 4-8mg PO QD MDD: 32mg/day	Tablet: 4mg, 8mg, 16mg, 32mg	**Angiotensin Receptor Blockers** • Preferred for ACEI-intolerant patients • Do not combine with ACEIs, sacubitril/valsartan, or aliskiren • May cause symptomatic hypotension with or without syncope • Hyperkalemia risk increased in CKD or if taking potassium or potassium-sparing drugs • Avoid if ascites due to cirrhosis or refractory ascites • Renal function may decline when initiating therapy; once therapy is established, renal dose adjustments generally not required	Y
Losartan (Cozaar)	Initial: 25-50mg PO QD MDD: 150mg/day	Tablet: 25mg, 50mg, 100mg		Y
Valsartan (Diovan)	Initial: 20-40mg PO BID MDD: 320mg/day	Tablet: 40mg, 80mg, 160mg, 320mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI)[7,9]				
Sacubitril/valsartan (Entresto)	Initial: ≥75 years old, not currently taking ACEI/ ARB, or previously taking low dose (ie, ≤10 mg/day enalapril, ≤160 mg/day valsartan or equivalent): 24mg/26mg PO BID Previously taking moderate to high dose ACEI/ARB (ie, >10mg/day enalapril, >160mg/day valsartan or equivalent): 49mg/51mg PO BID MDD: 194mg/206mg/day	Tablet: 24mg/26mg, 49mg/51mg, 97mg/103mg Note: strength expressed as sacubitril/valsartan	• Do not combine with aliskiren, additional ARB, or use within 36 hours of ACEI • Contraindicated if history of angioedema from any cause • Bioavailability of valsartan component of sacubitril/valsartan 40-60% higher than other formulations ; 26mg, 51mg, 103mg (as Entresto) equivalent to valsartan 40mg, 80mg, 160mg, respectively[31] • Doses expressed as a single strength (eg, 50mg, 100mg, 200mg) may refer to combined strengths of sacubitril and valsartan (ie, 24mg/26mg, 49mg/51mg, and 97mg/103mg, respectively) and should be clarified • Greater hypotensive effects and hyperkalemic effects in severe HFrEF compared to comparable doses of ACEIs/ARBs; do not initiate if BP <100mmHg • Requires renal/hepatic dose adjustments; avoid if severe hepatic impairment • Commonly causes hypotension, hyperkalemia, dizziness, cough	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BETA(β)-BLOCKERS[9]				
Bisoprolol (Zebeta)	Initial: 1.25mg PO QD MDD: 10mg/day	Tablet: 5mg, 10mg	**Beta-blockers** • Caution if asthma / COPD; may diminish efficacy of β_2-agonist bronchodilators or cause bronchospasm (esp. non-selective agents) • Use caution in patients with diabetes; can cause hyperglycemia and/or mask hypoglycemia symptoms • May cause bradycardia, fatigue; reduce dose if symptomatic bradycardia occurs • Avoid abrupt discontinuation; if deprescribing is warranted, taper over at least 1-2 weeks when possible **Bisoprolol, Carvedilol & Metoprolol succinate** • Beta-blockers with proven benefits in heart failure[7] • Caution in hepatic impairment; carvedilol is contraindicated if severe impairment **Bisoprolol & Metoprolol** • Preferred if asthma / COPD or concomitant bronchodilator use (β_1-selective agents) • Selectivity is lost at high doses **Carvedilol & Metoprolol** • ER capsules can be opened and contents sprinkled on small amount of soft food • Major CYP2D6 substrates **Carvedilol** • Non-selective beta-blocker; avoid if bronchospastic disease • Vasodilating properties; if symptomatic hypotension occurs, consider switching to an alternative agent • Administer with food to slow absorption, prevent orthostatic hypotension **Metoprolol** • Succinate form preferred; tartrate has not demonstrated the same benefits in clinical trials	Y
Carvedilol (Coreg)	Initial (IR): 3.125mg PO BID Initial (ER): 10mg PO QD MDD (IR): ≤85kg: 50mg/day >85kg: 100mg/day MDD (ER): 80mg/day	Capsule (ER): 10mg, 20mg, 40mg, 80mg Tablet: 3.125mg, 6.25mg, 12.5mg, 25mg		Y
Metoprolol succinate (Kapspargo, Toprol XL)	Initial: 12.5-25mg PO QD MDD: 200mg/day	Sprinkle capsule (ER): 25mg, 50mg, 100mg, 200mg Tablet (ER)*: 25mg, 50mg, 100mg, 200mg Note: IR / tartrate forms not preferred in HF		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DIURETICS - ALDOSTERONE ANTAGONISTS[9]				
Eplerenone (Inspra)	Initial: 25mg PO QAM MDD: 50mg/day	Tablet: 25mg, 50mg	**Aldosterone Antagonists** • Only medications known to improve both symptoms and quality of life in HFpEF[2] • Doses used in HF are generally lower than those typically needed to treat hypertension, ascites[7] • Increase serum potassium; effect can be beneficial to counteract potassium loss caused by loop diuretics • Risk factors for hyperkalemia include advanced age, diabetes, renal impairment, and concomitant potassium supplementation or ACEI / ARB therapy • Avoid potassium-containing salt substitutes • Avoid if CrCl <30ml/min or GFR ≤30 • Require renal dose adjustments • Administer in AM to avoid nocturia • May be given in divided doses QD-BID **Eplerenone** • Preferred if painful gynecomastia occurs with spironolactone (more common w/ males) • Major CYP3A4 substrate; many drug interactions, contraindicated with strong CYP3A4 inhibitors **Spironolactone** • If potassium is monitored, doses up to 25mg/day can be administered in patients receiving dialysis • Maximum diuretic effect may be delayed (2-3 days) • Food increases bioavailability; give consistently with regard to food • Oral suspension is expensive and not therapeutically equivalent to tablets (suspension increases serum concentration by 15-37%)	Y
Spironolactone (Aldactone)	Initial: 12.5-25mg PO QAM MDD: 25mg (elderly) to 50mg/day (divided QD or BID)	Oral suspension: 25mg/5ml Tablet: 25mg, 50mg, 100mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DIURETICS - LOOP[9,32]				
Bumetanide (Bumex)	Initial (PO/IV): 0.5mg QAM-BID MDD: 10mg/day	Solution for injection: 0.25mg/ml Tablet: 0.5mg, 1mg, 2mg	**Loop Diuretics** • Preferred diuretics for symptomatic HF • Combination with thiazide diuretics can be useful in diuretic resistant patients • Higher doses are generally required in CKD / decompensation and are associated with toxicity; do not exceed MDD[34] • Once an effective dose is established, further dose titration does not typically produce additional diuresis, rather the dosing frequency should be increased.[5,6] • If a dose is not effective, increase the dose and not the frequency.[5] • Parenteral or sublingual routes may be more effective during exacerbations due to physiologic changes affecting GI drug absorption[3-5] • Oral dose equivalence described, but consider starting alternate diuretic at initial dose if switching due to possible "Lasix resistance" » Normal renal function: **furosemide** 40mg ≈ **bumetanide** 1mg ≈ **torsemide** 10-20mg ≈ **ethacrynic acid** 50mg » Renal impairment: **furosemide** 20mg ≈ **bumetanide** 1mg • Associated with hypotension and electrolyte abnormalities (hypokalemia, hyponatremia, hyperuricemia); evidence to support co-prescribing potassium supplementation is limited **Bumetanide & Torsemide** • More predictable bioavailability / absorption than furosemide; preferred if failure to respond to furosemide • PO : IV ≈ 1mg : 1mg *(Continued on next page)*	Y
Ethacrynic acid (Edecrin)	Initial (PO/IV): 50mg QAM (25mg-50mg if elderly) MDD (PO): 400mg/day MDD (IV): not established	Solution for injection: 50mg Tablet: 25mg		Y
Furosemide[33] (Lasix)	Initial (PO/SL/IV/SQ/IM): 20mg QAM-BID MDD: 600mg/day	Oral solution: 8mg/ml, 10mg/ml Solution for injection: 10mg/mL Tablet: 20mg, 40mg, 80mg		Y
Torsemide (Demadex)	Initial: 5mg PO QAM MDD: 200mg/day	Tablet: 5mg, 10mg, 20mg, 100mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DIURETICS - LOOP (CONTINUED)[9,32]				
			Bumetanide • Safety / efficacy of SQ administration not established[33] **Ethacrynic acid** • Reserve for patients who develop hypersensitivity / allergy to other loop diuretics • Ototoxicity more common at higher doses vs. other loop diuretics • Expensive **Furosemide** • Wide interpatient variability in bioavailability / response • Give on an empty stomach • PO : IV ≈ 1-2mg : 1mg • SQ » In decompensated patients, reduces symptoms and rehospitalizations, facilitates wishes to die at home[35] » Can restore oral diuretic bioavailability in decompensated patients within days[36,37] » Initial dose is same as previous oral dose[38] » Onset = 30 min., Duration = 4 hours[38] » Titrate dose by 50% if not achieving ≥ 1kg/day weight loss after 48 hours[38] » Relatively dilute solution for injection (10mg/ml) often necessitates use of multiple sites or continuous subcutaneous infusion (CSCI)[38] » Adverse effects are typically mild and tolerable; the solution for injection has alkaline pH (8.5-9) which is likely responsible for transient local skin reactions, erythema, irritation, itching, and discomfort[35,36,38-40] » Injection sites in the pectoral region better tolerated than in extremities[40] » Slowing the rate of injection and rotating injection sites may improve tolerability[41] • SL[4] » 12% more bioavailable than oral dosing » Keep tablet under tongue for 5 min. without eating or drinking » Eliminates need for gut absorption, which is compromised in acute decompensated heart failure; as such, may have utility in decompensated patients	

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DIURETICS - THIAZIDE[9,15]				
Chlorothiazide (Diuril)	Initial: 250-500mg PO QAM-BID MDD: 1,000mg/day	Oral suspension: 250mg/5ml	**Thiazide Diuretics** • Add-on diuretic (typically metolazone) for patients who fail to respond to ceiling doses of loop diuretics; commonly administered 30-60 min. before loop diuretic to promote sequential diuresis[15,42] • May cause photosensitivity • Associated with dose-dependent electrolyte / metabolic abnormalities (hypokalemia, hyponatremia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia) • Most cases of diuretic-induced hyponatremia attributed to thiazides; if suspected, consider deprescribing • Higher risk for dehydration when used in combination with loop diuretics; monitor as consistent with plan of care • Unless combined with a loop diuretic, efficacy is generally reduced in significant renal impairment (eg, CrCl <30ml/min) • Caution in renal / hepatic impairment • Administer in AM to avoid nocturia **Chlorothiazide, Chlorthalidone** • Ineffective if CrCl <10ml/min; diminished effects if CrCl <30ml/min **Chlorothiazide** • Ineffective if CrCl <30ml/min unless combined with loop diuretic **Chlorthalidone** • Effects may be more pronounced after several days, once steady-state achieved **HCTZ** • Ineffective if CrCl <30ml/min **Indapamide** • Most effective thiazide if CrCl <30ml/min • Renal dose adjustments suggested	Y
Chlorthalidone (Thalitone)	Initial: 12.5-25mg PO QAM or PRN on intermittent days MDD: 100mg/day	Tablet: 25mg, 50mg		Y
Hydrochlorothiazide (HCTZ) (Microzide)	Initial: 25-100mg PO divided QAM-BID (12.5mg QAM if elderly) BID dosing preferred by some experts MDD: 200mg/day	Capsule: 12.5mg Tablet: 12.5mg, 25mg, 50mg		Y
Indapamide (Lozol)	Initial: 2.5mg PO QAM BID dosing preferred by some experts MDD: 5mg/day	Tablet: 1.25mg, 2.5mg		Y
Metolazone (Zaroxolyn)	Initial: 2.5mg PO QAM MDD: 20mg/day	Tablet: 2.5mg, 5mg, 10mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
SGLT-2 INHIBITORS[7,9]				
Dapagliflozin (Farxiga)	Initial: 10mg PO QD MDD: same as initial dosing	Tablet: 5mg, 10mg	**SGLT-2 inhibitors** • Useful for HF patients with or without diabetes • If used with sulfonylureas or insulin, dose reductions may be necessary to prevent hypoglycemia • Can cause dehydration / hypotension; risk increased if elderly, renal impairment • UTI, and genitourinary fungal infections are adverse effects • Fever or malaise accompanied by genital or perianal pain, tenderness, swelling should prompt suspicion of Fournier gangrene (a rare, but potentially fatal infection) • Nausea / vomiting should prompt suspicion of diabetic ketoacidosis (DKA) • Expensive **Dapagliflozin** • Contraindicated if GFR <30 **Empagliflozin** • Contraindicated if GFR <20	Y
Empagliflozin (Jardiance)	Initial: 10mg PO QD MDD: same as initial dosing	Tablet: 10mg, 25mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER[9]				
Isosorbide dinitrate/ hydralazine (BiDil)	Initial: one tablet (20mg/37.5mg) PO TID MDD: six tablets (120mg/225mg)/day	Tablet: 20mg/37.5mg Note: strength expressed as isosorbide dinitrate/ hydralazine	• First-line therapy for self-identified African Americans; more significant benefits observed in these patients • Medications can be prescribed individually as substitution for combination tablet[7] • Add or titrate diuretics if hydralazine-induced fluid retention occurs • Can cause severe hypotension accompanied by paradoxical bradycardia and increased angina • Peripheral neuritis (eg, paresthesia, numbness, tingling) is possibly related to antipyridoxine effects of hydralazine; vitamin B6 supplementation can be considered • Nitrate tolerance less concerning when combined with hydralazine	Y
Digoxin (Digitek, Lanoxin)	Initial: 0.125-0.25mg PO QD MDD: not established; doses >0.25mg/day rarely used	Oral solution: 0.05mg/ml Tablet: 0.0625mg, 0.125mg, 0.25mg	• Second-line, add-on therapy • Narrow therapeutic index • Drug toxicity is a common cause of ED visits, especially if female or >85 years old[43] • Doses as low as 0.125mg QOD should be considered if elderly, low body mass, or reduced renal clearance due to risk for toxicity • Signs / symptoms of toxicity include visual disturbances (blurred vision, yellow vision, halos), arrhythmia, GI symptoms (nausea, vomiting, diarrhea, abdominal pain), delirium, and headache • Additive effects when combined with bradycardia-causing drugs • 0.0625mg tablets expensive *(Continued on next page)*	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER (CONTINUED)[9]				
Ivabradine[7,8] (Corlanor)	Initial: 2.5-5mg PO BID MDD: 15mg/day	Oral solution: 5mg/5ml Tablet: 5mg, 7.5mg	• Second-line, add-on therapy for patients with EF ≤35%, in normal sinus rhythm, and with resting HR ≥70 bpm despite optimally titrated beta-blockers • Contraindicated if HFpEF, angina with normal ejection fraction, severe hepatic impairment, acute HF decompensation, hypotension, bradycardia, persistent Afib/AFlu, sick sinus syndrome or 3rd degree heart block without pacemaker • Causes QT prolongation • Adjust dose to resting HR 50-60bpm • Commonly causes bradycardia, blurred vision[7] • Expensive	Y
INTRAVENOUS (IV) INOTROPES[9,11,23,28]				
Dobutamine (Dobutrex)	Initial (CIVI): 1-2.5mcg/kg/min Usual maintenance dose: 2.5-10mcg/kg/min MDD: 40mcg/kg/min (see notes)	Solution for injection: 1mg/ml, 2mg/ml, 4mg/ml, 250mg/20ml, 500mg/40ml	**IV Inotropes** • Require central venous access • Adverse effects include hypotension, arrhythmia, tachycardia, angina, headache • Use the minimum dose necessary to improve symptoms • Tapering protocols exist (**Figure 2**) • Expensive **Dobutamine** • More likely to cause hypertension, tachyphylaxis • May be temporarily administered through peripheral venous access; central venous access required for long term therapy • Diminished benefit and increasing toxicity when doses of 10-20mcg/kg/min are exceeded.[15,24] **Milrinone** • Longer half-life than dobutamine • Requires renal dose adjustments; contraindicated in severe renal impairment	—
Milrinone (Primacor)	Initial (CIVI): 0.125mcg/kg/min Usual maintenance dose: 0.125-0.375mcg/kg/min MDD: 0.75mcg/kg/min	Solution for injection: 200mcg/ml, 10mg/10ml, 20mg/20ml, 50mg/50ml		—

References

1. Zipes DP, et al. Braunwald's Heart Disease: A textbook of cardiovascular medicine. 11th ed. Philadelphia, PA: Elsevier; 2019.
2. McGuinty C, et al. Heart failure: A palliative medicine review of disease, therapies, and medications with a focus on symptoms, function, and quality of life. Journal of Pain & Symptom Management. 2020;59(5):1127-1146.
3. Romeiro FG, et al. Gastrointestinal changes associated to heart failure. Arquivos Brasileiros de Cardiologia. 2012;98(3):273-277.
4. Haegeli L, et al. Sublingual administration of furosemide: new application of an old drug. British Journal of Clinical Pharmacology. 2007;64(6):804-809.
5. Brater DC, et al. Causes and treatment of refractory edema in adults. UpToDate (Lit review current through Oct 2020, accessed Oct 2020).
6. Cho S, et al. Peripheral edema. American Journal of Medicine. 2002;113:580-586.
7. Maddox TM, et al. 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment. JACC. 2021;77(6):772-810.
8. Butler J, et al. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. European Heart Journal. 2021;42(13):1203-1212.
9. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.
10. Page RL, et al. Drugs that may cause or exacerbate heart failure. American Heart Association. 2016;134(6):E32-E69.
11. Ginwalla M, et al. Current status of inotropes in heart failure. Heart Failure Clinics. 2018;14:601-616.
12. Orr K, et al. Psychostimulants in the treatment of depression: A review of the evidence. CNS Drugs. 2007;21(3):239-257.
13. Borlaug BA, et al. Treatment and prognosis of heart failure with mid-range ejection fraction. UpToDate. (Lit review current through Feb 2020, accessed March 2020).
14. Gramsky C, et al. Outpatient management of chronic heart failure. Critical Care Nursing Clinics of North America. 2003;15:501-509.
15. Yancy CW, et al.; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):e240-e327.
16. de Vries RJ, et al. Efficacy and safety of calcium channel blockers in heart failure: focus on recent trials with second-generation dihydropyridines. Am Heart Journal. 2000;139(2 Pt 1):185-194.
17. Colucci WS. Secondary pharmacologic therapy in heart failure with reduced ejection fraction (HFrEF) in adults. UpToDate (Lit review current through Feb 2020, accessed March 2020).
18. McMurray JJV, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. New England Journal of Medicine. 2014;371:993-1004.
19. American College of Cardiology. LIFE: Sacubitril/valsartan not superior to valsartan in advanced HFrEF. Published May 17, 2021. Accessed online at: https://www.acc.org/Latest-in-Cardiology/Articles/2021/05/12/19/40/Mon-8am-LIFE-acc-2021
20. Kosiborod MN, et al. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: Results from the DAPA-HF trial. Circulation. 2020;141:90-99,
21. Nassif ME, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. Circulation. 2019;140(18):1463-1476.
22. McMurray JJV, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine. 2019;381;1995-2008.
23. Chuzi S, et al. Palliative inotrope therapy: a narrative review. JAMA Cardiology. 2019;4(8):815-822.
24. López-Candales A, et al. Need for hospice and palliative care services in patients with end-stage heart failure treated with intermittent infusion of inotropes. Clinical Cardiology. 2003;27(1):23-28.
25. Holder R, et al. GET PUMPED! Palliative inotropes in advanced heart failure across the continuum of care. 2016 AAHPM & HPNA Annual Assembly.
26. Rich MW, et al. Dobutamine for patients with end-stage heart failure in a hospice program? Journal of Palliative Medicine. 2003;6(1):93-97.
27. Overgaard CB, et al. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. Circulation. 2008;118(10):1047-56.
28. Groninger H, et al. Weaning continuous cardiac inotropes at end of life: case studies and institutional clinical guidelines. Journal of Pain and Symptom Management. 2020;60(1):170-175.
29. Current wholesaler prices (Accessed 11/13/20)
30. Beets MT, et al. Urgent implantable cardioverter defibrillator deactivation by unconventional means. Journal of Pain and Symptom Management. 2011;42(6):941-945.
31. Lexicomp Online, AHFS DI – Sacubitril and Valsartan. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.
32. Table: Loop diuretic doses for adult patients with common causes of edema. UpToDate. 2021.
33. Jozwiak R, et al. Fast Fact #353: Subcutaneous diuretics for end-of-life management of heart failure. Accessed online at: https://www.mypcnow.org/fast-fact/subcutaneous-diuretics-for-end-of-life-management-of-heart-failure/
34. Brater DC, et al. Loop diuretics: Dosing and major side effects. UpToDate (Lit review current through April 2021, accessed May 2021).
35. Zacharias H et al. Is there a role for subcutaneous furosemide in the community and hospice management of end-stage heart failure? Palliative Medicine. 2011;25(6):658-63.
36. Sica D, et al. Subcutaneous furosemide in heart failure – Pharmacokinetic characteristics of a newly buffered solution. JACC: Basic to Translational Science. 2018;3(1):25-34.
37. Afari M, et al. Subcutaneous furosemide for the treatment of heart failure: a state of the art review. Heart Failure Reviews. 2019;24:309-313.
38. Carone L, et al. Therapeutic reviews: Furosemide. Journal of Pain & Symptom Management. 2016;52(1):144-50.
39. Francis G, et al. Furosemide reimagined – novel subcutaneous formulation for a 50-year-old loop diuretic agent for the treatment of acute decompensated heart failure, JACC: Heart Failure, 2018;6(1):71-72.
40. Goenaga M, et al. Subcutaneous furosemide (letter to editor). The Annals of Pharmacotherapy. 2004;38(October):1751.
41. Verma A, et al. Diuretic effects of subcutaneous furosemide in human volunteers: a randomized pilot study. The Annals of Pharmacotherapy. 2004;38(April):544-549.
42. Shore S. 2021 Expert Decision Pathway for HFrEF Treatment Optimization. January 2021. Accessed online at: https://www.acc.org/Latest-in-Cardiology/ten-points-to-remember/2021/01/2021/21/56/2021-Update-Expert-Consensus-for-HFrEF
43. See I, et al. Emergency department visits and hospitalizations for digoxin toxicity – United States, 2005 to 2010. Circulation: Heart Failure. 2014;7:28-34.

Hypertension

DEFINITIONS[1,2]

Hypertension (HTN) is a state of persistently elevated blood pressure (BP), generally defined as BP ≥ 130/80 mmHg.

- **Primary (or essential) HTN:** no known cause; possibly related to genetics, environment, or diet
- **Secondary HTN:** due to a known, specific cause (usually a renal, adrenal, or hormonal disorder)
- **Isolated systolic hypertension:** SBP ≥160 mmHg / DBP ≤90 mmHg; the predominant form of HTN in older patients, related to age-related arterial stiffening

Hypertensive crisis is a state of severely elevated BP (>180/120 mmHg).

- **Hypertensive urgency:** asymptomatic and no evidence of target organ damage; may be related to medication noncompliance or excess sodium consumption
- **Hypertensive emergency (HE):** acute, marked elevation in BP with signs / symptoms of damage to target organs including brain, heart, kidney, retina, blood vessels (eg, intracerebral hemorrhage, ischemic stroke, MI, left ventricular failure with pulmonary edema, unstable angina, dissecting aortic aneurysm, acute renal failure)

ASSOCIATED SYMPTOMS

- HTN is generally an asymptomatic condition, except in cases of hypertensive emergency.[1,2]
- Symptoms of hypertensive emergency may include headache, dizziness, ataxia, unilateral numbness / weakness, aphasia, altered mental status, dyspnea, chest pain, peripheral edema, reduced urine output, vomiting, or vision changes.[3]

CLINICAL INSIGHTS

- Traditional aims of HTN treatment are to reduce cardiovascular morbidity and mortality. In most cases, tight blood pressure control does not confer short-term benefits and is inconsistent with end-of-life goals of care.
- Clinical judgment should be used to determine if antihypertensives should be continued in patients at risk for developing a hypertensive crisis.
  - » Hypertensive urgencies are not associated with adverse short-term outcomes.[4]
  - » There is no strong evidence that antihypertensive treatment of HE affects morbidity and mortality; however, from clinical experience many consider drug therapy beneficial in HE.[1]
- When prescribed to palliate symptoms (eg, heart failure, arrhythmia, angina) antihypertensives should be continued for as long as the patient desires or tolerates.

GOALS OF THERAPY & LIBERALIZING TREATMENT TARGETS

- The primary goal of therapy in the hospice setting is to reduce risks and burdens (eg, adverse effects, polypharmacy) associated with drug therapy and intensive BP lowering by rationally deprescribing antihypertensive drugs.[1]
  - » Those with multimorbidity, fall history, cognitive impairment, advanced age, dehydration, frailty, and clinical decline are more susceptible.[1]
  - » Hospice patients and many older adults are more likely to experience harm related to treating to SBP <140 mmHg or DBP <60 mmHg.[5]
- HTN treatment guidelines recommend individualizing BP targets (no specific target defined) for patients ≥65 years old, high burden of comorbidity, and limited life expectancy.[1]
  - » Guidelines also endorse the use of less intensive targets for patients with CKD at end-of-life.[6,7]
- A target SBP of 140 to 160 mmHg has been suggested for patients >80 years old with limited life expectancy since they are most likely to experience harm when treated more aggressively and because patients with chronic HTN are often more tolerant of higher BP.[1,5]

DEPRESCRIBING

- Deprescribing one or more antihypertensives in older adults has the potential to improve quality of life and survival.[5,8,9]
- Patients should be informed about the risks of antihypertensive treatment and presented with opportunities for deprescribing through the process of shared decision-making. Many prioritize the prevention of fall-related injuries over cardiovascular risk reduction.[10]
- Consider presence of adverse effects when deprescribing antihypertensives (**Table 1**).
- Deprescribing drugs known to exacerbate HTN can facilitate antihypertensive deprescribing.[1]
  - » Drugs that increase BP include amphetamines, atypical antipsychotics, cyclosporine, antidepressants (SNRIs, MAOIs, TCAs), caffeine, decongestants, herbal products (eg, MaHuang / ephedra, St. John's Wort), NSAIDs, and corticosteroids.
- In very elderly patients receiving antihypertensives, deprescribing one antihypertensive has been shown to be well tolerated without impacting BP control.[12]
- Abruptly discontinuing certain antihypertensives is more likely to cause rebound HTN and symptomatic withdrawal including nervousness, agitation, headache, and tremors (**Table 2**).[11,13]
  - » If symptomatic HTN occurs following discontinuation, treatment reinstatement can be considered.

TABLE 1: ANTIHYPERTENSIVE ADVERSE EFFECTS[11]

Drug / Drug Class	Common and Notable Adverse Effects
All	Hypotension
ACEIs	Cough, angioedema, hyperkalemia, GFR reduction
Aldosterone antagonists	Electrolyte imbalance (esp. hyperkalemia), dehydration, gynecomastia (spironolactone)
$Alpha_1$ blockers	Orthostatic hypotension, syncope, dizziness, fatigue, edema, nasal congestion, priapism, headache (esp. doxazosin, prazosin)
$Alpha_2$ agonists	Orthostatic hypotension, dizziness, bradycardia, fatigue, headache, abdominal pain, xerostomia (esp. clonidine)
ARBs	Hyperkalemia, diarrhea / weight loss (olmesartan), GFR reduction
Beta-blockers	Fatigue, bradycardia, hyperglycemia, bronchospasm (esp. non-selective agents)
CCBs (DHP)	Peripheral edema, headache, dizziness, lightheadedness, flushing
CCBS (Non-DHP)	Peripheral edema, headache, constipation (esp. verapamil), bradycardia
Hydralazine	Edema, tachycardia, anorexia, nausea, vomiting, diarrhea, headache, dizziness, tremor
Loop diuretics	Electrolyte imbalance (esp. hypokalemia), dehydration, AKI, hyperuricemia / gout, hearing loss, tinnitus, severe skin reactions
Thiazide diuretics	Electrolyte imbalance, dehydration, hyperuricemia / gout, hyperglycemia, myopia, glaucoma, photosensitivity, severe skin reactions
Triamterene	Electrolyte imbalance (esp. hyperkalemia), dehydration, hyperuricemia / gout, hyperglycemia, photosensitivity, rash

TABLE 2: SUGGESTED TAPERING SCHEDULES FOR WITHDRAWING SELECT ANTIHYPERTENSIVES[11,13,14]

Drug / Drug Class	Suggested Taper	Notes
Clonidine*	Taper over at least 6-10 days, decreasing dose by ⅓ to ½ every 2-3 days	• Rebound HTN more common with higher oral doses • If rebound HTN occurs after gradual taper, restarting therapy should provide nearly immediate relief
Alpha$_1$ blockers	Ideally, taper over at least 1 week	• However, data from BPH trials show that abrupt discontinuation of peripherally-acting agents (terazosin, prazosin, doxazosin) is feasible and safe
Beta-blockers*†	Gradually taper over at least 1-2 weeks **Drugs with shorter half-lives (ie, dosed ≥2 times per day)** Take usual dose QD x 1 week, then QOD x 1 week, then d/c **Drugs with longer half-lives (ie, dosed QD)** ½ of usual dose QD x 1 week, then QOD x 1 week, then d/c; accelerated tapers can be accomplished in 1 week, if necessary	• If angina or other ischemic symptoms develop, reinstate at previous dose and reattempt taper at slower rate • Withdrawal symptoms are less likely with longer-acting agents (eg, atenolol or nadolol)

*If clonidine and beta-blocker withdrawal are indicated, sequential tapers of each are recommended. Gradually taper and deprescribe beta-blocker first (starting several days before clonidine withdrawal), follow with gradual clonidine taper.

†Abrupt beta-blocker withdrawal may also be associated with angina, MI, and sudden death.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ALPHA$_1$(α_1) BLOCKERS[11]				
Doxazosin (Cardura)	Initial (IR): 1mg PO QD MDD: 16mg/day	Tablet: 1mg, 2mg, 4mg, 8mg	**Alpha$_1$ Blockers (nonselective)** • Use cautiously in geriatric patients due to risk for orthostatic and first-dose hypotension, possibly resulting in syncope • Often given at bedtime to limit orthostatic hypotension • Hypotension risk increased when combined with PDE-5 inhibitors • Additional adverse effects include priapism, edema, and nasal congestion • Caution in HF • Avoid abrupt discontinuation; taper over at least 1 week when possible (**Table 2**) • Generally reserved for patients with comorbid BPH who fail to respond to other antihypertensives	Y
Prazosin (Minipress)	Initial: 1mg PO BID-TID MDD: 40mg/day	Capsule: 1mg, 2mg, 5mg		Y
Terazosin (Hytrin)	Initial: 1mg PO QD MDD: 20mg/day	Capsule: 1mg, 2mg, 5mg, 10mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ALPHA$_2$(α_2) AGONISTS[1,11]				
Clonidine (Catapres, Catapres-TTS)	Initial (PO): 0.1mg PO QD-BID Initial (transdermal): 0.1mg/24hr patch applied topically and changed every 7 days MDD (PO): 2.4mg/day; doses >0.6mg/day not generally used MDD (transdermal): 0.3mg/day	Tablet: 0.1mg, 0.2mg, 0.3mg Transdermal patch*: 0.1mg/24hr, 0.2mg/24hr, 0.3mg/24hr	**Alpha$_2$ Agonists** • Adverse effects include abdominal pain, xerostomia (esp. clonidine), dizziness, drowsiness, headache • Caution in geriatric patients due to risk for adverse CNS effects (esp. sedation), bradycardia, orthostatic hypotension • Caution in renal impairment; dose adjustments may be necessary **Clonidine** • Avoid abrupt discontinuation; taper over at least 6-10 days when possible (**Table 2**) • Rebound hypertension / withdrawal less likely with transdermal formulation • Patch » Apply to clean, hairless area of upper outer arm or chest; rotate application site weekly » Dispensed with optional, pharmaceutically inactive adhesive cover » *Patches cannot be cut, but partial doses can be administered by blocking patch surface area proportionally with an adhesive bandage » Dispose by folding adhesive ends together and discarding in trash out of reach from children / pets » Onset delayed by 2-3 days after initial application » More expensive than tablets; may be beneficial to facilitate drug taper and for patients unable to use the oral route • Dosage form conversions » Tablet → patch: overlap therapy for 1-3 days while gradually reducing PO dose due to delayed onset of patch » Patch → tablet: consider initiating conservative PO doses within 8 hours of patch removal and gradually titrate dose upwards; therapeutic levels will persist for approx. 8 hours and up to 48 hours after patch removal **Methyldopa** • Chronic use may cause sodium and water retention necessitating treatment with loop diuretics	Y
Guanfacine (Tenex)	Initial: 0.5-1mg PO QHS MDD: 2mg/day	Tablet: 1mg, 2mg		Y
Methyldopa (Aldomet)	Initial: 250mg PO BID-TID (NTE 500mg/day if concomitant antihypertensive use) MDD: 3,000mg/day			Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs)[11]				
Benazepril (Lotensin)	Initial: 5-10mg PO QD MDD: 40mg/day	Tablet: 5mg, 10mg, 20mg, 40mg	**ACE-Inhibitors** • Do not combine with ARBs, aliskiren, or take within 36 hours of sacubitril/valsartan • Angioedema involving the head, neck, or intestine can occur at any time during treatment and should prompt discontinuation • A dry, hacking, nonproductive cough is the most common adverse effect; it generally resolves within 1-4 weeks of discontinuation. Onset is variable; can occur up to 6 months after starting therapy. • Hyperkalemia risk increased in CKD or if taking potassium or potassium-sparing drugs • May cause symptomatic hypotension with or without syncope • Avoid if ascites due to cirrhosis or refractory ascites • Renal function may decline when initiating therapy; once therapy is established, renal dose adjustments may be required • Oral solutions are expensive	Y
Captopril (Capoten)	Initial: 12.5-25mg PO BID-TID MDD: 150mg/day	Tablet: 12.5mg, 25mg, 50mg, 100mg		Y
Enalapril (Epaned, Vasotec)	Initial: 5mg PO divided QD-BID MDD: 40mg/day	Oral solution: 1mg/ml Tablet: 2.5mg, 5mg, 10mg, 20mg		Y
Fosinopril (Monopril)	Initial: 10mg PO QD MDD: 80mg/day	Tablet: 10mg, 20mg, 40mg		Y
Lisinopril (Prinivil, Qbrelis, Zestril)	Initial: 5-10mg PO QD MDD: 40mg/day	Oral solution: 1mg/ml Tablet: 2.5mg, 5mg, 10mg, 20mg, 30mg, 40mg		Y
Moexipril (Univasc)	Initial: 3.75-7.5mg PO QD MDD: 30mg/day	Tablet: 7.5mg, 15mg		Y
Perindopril (Aceon)	Initial: 4mg PO QD MDD: 16mg/day	Tablet: 2mg, 4mg, 8mg		Y
Quinapril (Accupril)	Initial: 10-20mg PO QD MDD: 80mg/day	Tablet: 5mg, 10mg, 20mg, 40mg		Y
Ramipril (Altace)	Initial: 2.5mg PO QD MDD: 20mg/day	Capsule: 1.25mg, 2.5mg, 5mg, 10mg		Y
Trandolapril (Mavik)	Initial: 1mg PO QD MDD: 4mg/day	Tablet: 1mg, 2mg, 4mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)[11]				
Azilsartan (Edarbi)	Initial: 40mg PO QD MDD: 80mg/day	Tablet: 40mg, 80mg	**Angiotensin Receptor Blockers** • Preferred for ACEI-intolerant patients • Do not combine with ACEIs, sacubitril/ valsartan, or aliskiren • May cause symptomatic hypotension with or without syncope • Hyperkalemia risk increased in CKD or if taking potassium or potassium-sparing drugs • Avoid if ascites due to cirrhosis or refractory ascites • Renal function may decline when initiating therapy; once therapy is established, renal dose adjustments generally not required (except olmesartan)	Y
Candesartan (Atacand)	Initial: 8mg PO QD MDD: 32mg/day	Tablet: 4mg, 8mg, 16mg, 32mg		Y
Irbesartan (Avapro)	Initial: 150mg PO QD MDD: 300mg/day	Tablet: 75mg, 150mg, 300mg		Y
Losartan (Cozaar)	Initial: 25-50mg PO QD MDD: 100mg/day	Tablet: 25mg, 50mg, 100mg		Y
Olmesartan (Benicar)	Initial: 20mg PO QD MDD: 40mg/day (20mg/day if CrCl <40ml/min)	Tablet: 5mg, 20mg, 40mg		Y
Telmisartan (Micardis)	Initial: 20-40mg PO QD MDD: 80mg/day	Tablet: 20mg, 40mg, 80mg		Y
Valsartan (Diovan)	Initial: 80-160mg PO QD MDD: 320mg/day	Tablet: 40mg, 80mg, 160mg, 320mg		Y
ANGIOTENSIN SYSTEM BLOCKER / RENIN INHIBITOR[11]				
Aliskiren (Tekturna)	Initial: 150mg PO QD MDD: 300mg/day	Tablet: 150mg, 300mg	• Causes hyperkalemia • Do not combine with ACEI or ARB (esp. if diabetes or CrCl <60ml/min); associated with increased incidence of renal impairment, hypotension, and hyperkalemia	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BETA(β)-BLOCKERS[1,11,15,16]				
Acebutolol (Sectral)	Initial: 200-400mg PO divided QD-BID MDD: 1,200mg/day (800mg/day for geriatric patients)	Capsule: 200mg, 400mg	**Beta-Blockers** • Caution if asthma / COPD; may diminish efficacy of β_2-agonist bronchodilators or cause bronchospasm (esp. non-selective agents) • Use caution in patients with diabetes; can cause hyperglycemia and / or mask hypoglycemia symptoms • May cause bradycardia, fatigue; reduce dose or deprescribe if symptomatic bradycardia occurs • Avoid abrupt discontinuation; taper over at least 1-2 weeks when possible (**Table 2**) • Generally reserved for patients with comorbid arrhythmia, ischemic heart diseases or heart failure **Acebutolol, Bisoprolol, Carvedilol, Labetalol, Metoprolol, Nebivolol, Pindolol, Propranolol, Timolol** • Caution in hepatic impairment; carvedilol and nebivolol are contraindicated if severe impairment **Acebutolol, Atenolol, Nadolol, Nebivolol, Pindolol, Timolol** • Caution in renal impairment; acebutolol, atenolol, and nadolol require renal dose adjustment **Acebutolol, Atenolol, Betaxolol, Bisoprolol, Metoprolol, Nebivolol** • Preferred if asthma / COPD or concomitant bronchodilator use (β_1-selective agents) • Selectivity is lost at high doses	Y
Atenolol (Tenormin)	Initial: 25mg PO QD-BID MDD: 100mg/day	Tablet: 25mg, 50mg, 100mg		Y
Betaxolol (Kerlone)	Initial: 5-10mg PO QD MDD: 20mg/day	Tablet: 10mg, 20mg		Y
Bisoprolol (Zebeta)	Initial: 2.5-5mg PO QD MDD: 20mg/day	Tablet: 5mg, 10mg		Y
Carvedilol (Coreg, Coreg CR)	Initial (IR): 3.125-6.25mg PO BID Initial (ER): 20mg PO QD MDD (IR): 50mg/day MDD (ER): 80mg/day	Capsule (ER): 10mg, 20mg, 40mg, 80mg Tablet: 3.125mg, 6.25mg, 12.5mg, 25mg		Y
Labetalol (Trandate)	Initial: 100mg PO BID MDD: 800mg/day; doses up to 2,400mg/day may be needed for severe / resistant HTN	Tablet: 100mg, 200mg, 300mg		Y
Metoprolol (Kapspargo, Lopressor, Toprol XL)	Initial (IR): 50mg PO BID Initial (ER): 25-100mg PO QD MDD (IR, ER): 400mg/day	Capsule (ER): 25mg, 50mg, 100mg, 200mg Tablet: 25mg, 37.5mg, 50mg, 75mg, 100mg Tablet (ER)*: 25mg, 50mg, 100mg, 200mg		Y/N*
Nadolol (Corgard)	Initial: 40mg PO QD MDD: 320mg/day	Tablet: 20mg, 40mg, 80mg		Y

(Continued on next page)

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BETA(β)-BLOCKERS (CONTINUED)[1,11,15,16]				
Nebivolol (Bystolic)	Initial: 5mg PO QD MDD: 40mg/day	Tablet: 2.5mg, 5mg, 10mg, 20mg	**Carvedilol, Nadolol, Pindolol, Propranolol, Sotalol, Timolol** • Non-selective beta-blockers; avoid if bronchospastic disease **Carvedilol, Labetalol, Nebivolol** • Vasodilating properties; if symptomatic hypotension occurs, consider switching to an alternative agent **Acebutolol & Pindolol** • Minimal effects on resting heart rate compared to other beta-blockers (intrinsic sympathomimetic activity) **Carvedilol & Labetalol** • Mixed alpha- / beta-blocking activity; may be better tolerated than other non-selective agents in patients with respiratory disease[15] **Carvedilol & Metoprolol** • ER capsules can be opened and contents sprinkled on small amount of soft food • Major CYP2D6 substrates **Carvedilol** • Administer with food to slow absorption, prevent orthostatic hypotension **Pindolol** • Edema is a common adverse effect **Propranolol** • IR tablets should be taken on an empty stomach • Bioavailability approximately doubled in elderly patients; more conservative doses are reasonable	Y
Pindolol (Visken)	Initial: 5mg PO BID MDD: 60mg/day	Tablet: 5mg, 10mg		Y
Propranolol (Inderal, Inderal LA, InnoPran XL)	Initial (IR): 80mg PO divided BID-QID Initial (ER): 80mg PO QD MDD: 640mg/day 16 (HTN guidelines recommend significantly lower MDD of 160mg/day)	Capsule (ER)*: 60mg, 80mg, 120mg, 160mg Oral solution: 20mg/5ml, 40mg/5ml Tablet: 10mg, 20mg, 40mg, 60mg, 80mg		Y/N*
Timolol (Blocadren)	Initial: 10mg PO BID MDD: 60mg/day	Tablet: 5mg, 10mg, 20mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CALCIUM CHANNEL BLOCKERS (CCBs)[1,11,16,17]				
Amlodipine (Katerzia, Norvasc)	Initial: 2.5-5mg PO QD MDD: 10mg/day	Oral suspension: 1mg/ml Tablet: 2.5mg, 5mg, 10mg	**Calcium Channel Blockers** • Generally avoid in patients with HF; amlodipine and felodipine can be used if needed • Dose-dependent peripheral edema is common (esp. diltiazem, DHPs; females > males) • Headache is a common adverse effect • Major CYP3A4 substrates; many drug interactions • Grapefruit juice may increase drug levels; avoid if taking levamlodipine, nifedipine, nisoldipine **Dihydropyridines (DHPs)** • Amlodipine, felodipine, isradipine, levamlodipine, nicardipine, nifedipine, nisoldipine • May cause dizziness, light-headedness, flushing **Non-Dihydropyridines (Non-DHPs)** • Diltiazem, verapamil • Dose-dependent constipation is common (esp. verapamil) • Additive effects when combined with HR-lowering drugs • Moderate CYP3A4 inhibitors **Amlodipine, Diltiazem, Felodipine, Isradipine, Levamlodipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil** • Caution in hepatic impairment; verapamil requires dose adjustments **Diltiazem, Nicardipine, Verapamil** • Caution in renal impairment *(Continued on next page)*	Y
Diltiazem (Cardizem CD/LA, Cartia XT, Taztia XT, Tiazac)	Initial (ER, 12-hr): 60-120mg PO BID Initial (ER, 24-hr): 120-240mg PO QD MDD: 360mg/day	Capsule (ER, 12-hr)*: 60mg, 90mg, 120mg Capsule (ER, 24-hr)*: 120mg, 180mg, 240mg, 300mg, 360mg, 420mg Tablet: 30mg, 60mg, 90mg, 120mg Tablet (ER, 24-hr)*: 120mg, 180mg, 240mg, 300mg, 360mg, 420mg		Y/N*
Felodipine (Plendil)	Initial: 2.5-5mg PO QD MDD: not established; usually up to 10mg/day	Tablet (ER): 2.5mg, 5mg, 10mg		N
Isradipine (Dynacirc)	Initial: 2.5mg PO BID MDD: 20mg/day; limit to 10mg/day in older patients	Capsule: 2.5mg, 5mg		Y
Levamlodipine (Conjupri)	Initial: 1.25-2.5mg PO QD MDD: 5mg/day	Tablet: 2.5mg, 5mg		Y
Nicardipine (Cardene)	Initial: 20mg PO TID MDD: not established; usually up to 120mg/day	Capsule: 20mg, 30mg		Y
Nifedipine (Adalat CC, Afeditab CR, Nifediac CC, Nifedical XL, Procardia XL)	Initial (ER): 30-60mg PO QD MDD: 90-120mg/day	Tablet (ER): 30mg, 60mg, 90mg		N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CALCIUM CHANNEL BLOCKERS (CCBs) (CONTINUED)[1,11,16,17]				
Nisoldipine (Sular)	Initial (ER, original formula): 20mg PO QD; 10mg if geriatric Initial (ER, Geomatrix®): 17mg PO QD; 8.5mg if geriatric MDD (ER, original formula): not established; usually up to 40mg/day MDD (ER, Geomatrix®): 34mg/day	Tablet (ER, original formula): 20mg, 30mg, 40mg Tablet (ER, Geomatrix®): 8.5mg, 17mg, 25.5mg, 34mg	**Amlodipine** • Oral suspension is expensive **Diltiazem** • *Most ER formulations should not be crushed or opened (Taztia XT and Tiazac are exceptions) **Levamlodipine** • Expensive **Nifedipine** • IR formulation not recommended due to risk for severe hypotension • PM/HS dosing is associated with less edema than AM dosing[18] **Nisoldipine** • 34mg Geomatrix tablet is bioequivalent to 40mg ER tablet • Expensive (original formula > Geomatrix®) **Verapamil** • Associated with more hypotension than diltiazem • Delayed onset capsules should be dosed QD; other ER formulations can be given in BID divided doses • ER capsules can be opened and contents sprinkled on small amount of soft food • P-glycoprotein inhibitor • Can produce false-positive for presence of methadone in urine	N
Verapamil (Calan, Calan SR, Verelan, Verelan PM)	Initial (IR): 40-80mg PO TID Initial (ER): 120-180mg QD Initial (ER, delayed onset): 100-200mg QHS MDD (IR, ER): 480mg/day MDD (ER, delayed onset): 400mg/day	Capsule (ER): 120mg, 180mg, 240mg, 360mg Capsule (ER, delayed onset): 100mg, 200mg, 300mg Tablet: 40mg, 80mg, 120mg Tablet (ER)*: 120mg, 180mg, 240mg		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DIRECT VASODILATORS[11]				
Hydralazine (Apresoline)	Initial: 10mg PO QID MDD: 200-300mg/day; doses >200mg/day generally avoided due to risk of developing lupus-like syndrome	Tablet: 10mg, 25mg, 50mg, 100mg	**Direct Vasodilators** • Generally reserved for treatment-resistant hypertension • Often combined with a loop diuretic to prevent fluid retention / edema and a beta-blocker to prevent reflex tachycardia / angina exacerbations (esp. minoxidil) • Caution in HF **Hydralazine** • Contraindicated in CAD, mitral valve rheumatic disease • Caution if history of CVA, angina • Renal dose adjustments may be considered • Food increases bioavailability **Minoxidil:** • If supine diastolic BP is reduced by >30mmHg, give in divided doses • Caution in renal / hepatic impairment • Hypertrichosis (abnormal hair growth) and ECG changes are common	Y
Minoxidil (Loniten)	Initial: 5mg PO QD MDD: 100mg/day	Tablet: 2.5mg, 10mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DIURETICS – POTASSIUM SPARING[1,11]				
Amiloride (Midamor)	Initial: 5mg PO QAM MDD: 10mg/day	Tablet: 5mg	**Potassium-Sparing Diuretics** • Increase serum potassium; effect can be beneficial to counteract potassium loss caused by loop diuretics • Risk factors for hyperkalemia include advanced age, diabetes, renal impairment, and concomitant potassium supplementation or ACEI / ARB therapy • Avoid potassium-containing salt substitutes • Avoid if CrCl <30ml/min or GFR≤30 • Caution in hepatic impairment; triamterene contraindicated if severe impairment • Administer in AM to avoid nocturia • May be given in divided doses QD-BID **Eplerenone** • Preferred if painful gynecomastia occurs with spironolactone (more common w/males) • BID dosing often necessary for adequate BP reduction • Major CYP3A4 substrate; many drug interactions, contraindicated with strong CYP3A4 inhibitors **Spironolactone** • If potassium is monitored, doses up to 25mg/day can be administered in patients receiving dialysis • Food increases bioavailability; give consistently with regard to food • Oral suspension is expensive and not therapeutically equivalent to tablets (suspension increases serum concentration by 15-37%) **Triamterene** • May cause photosensitivity • Can increase uric acid levels, leading to gout • Abrupt discontinuation may cause rebound potassium excretion (kaliuresis); gradual withdrawal is recommended • More expensive as monotherapy (vs. combination with hydrochlorothiazide)	Y
Eplerenone (Inspra)	Initial: 50mg PO QAM MDD: 100mg/day	Tablet: 25mg, 50mg		Y
Spironolactone (Aldactone)	Initial: 12.5-25mg PO QAM MDD: 100mg/day	Oral suspension: 25mg/5ml Tablet: 25mg, 50mg, 100mg		Y
Triamterene (Dyrenium)	Initial: 50mg PO QAM MDD: 100mg/day	Capsule: 50mg, 100mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DIURETICS – THIAZIDES [1,11]				
Chlorothiazide (Diuril)	Initial: 500mg PO QAM MDD: not established; usually up to 2,000mg/day	Oral suspension: 250mg/5ml	**Thiazide Diuretics** • More persistent antihypertensive effects than loop diuretics; may be preferred for hypertensive patients with mild fluid retention • May cause photosensitivity • Associated with dose-dependent electrolyte / metabolic abnormalities (hypokalemia, hyponatremia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia) • Most cases of diuretic-induced hyponatremia attributed to thiazides; if suspected, consider deprescribing • Higher risk for dehydration when used in combination with loop diuretics; monitor as consistent with plan of care • Caution in renal / hepatic impairment • Administer in AM to avoid nocturia **Chlorothiazide & Chlorthalidone** • Ineffective if CrCl <10ml/min; diminished effects if CrCl <30ml/min **Chlorthalidone & HCTZ** • Doses >25mg/day may cause more adverse effects and unlikely to produce additional improvements in BP **Chlorothiazide** • Ineffective if CrCl <30ml/min unless combined with loop diuretic **Chlorthalidone** • Effects may be more pronounced after several days, once steady-state achieved **HCTZ** • Ineffective if CrCl <30ml/min **Indapamide** • Most effective thiazide if CrCl <30ml/min • Renal dose adjustments suggested	-
Chlorthalidone (Thalitone)	Initial: 6.25mg (elderly) to 12.5 PO QAM MDD: not established; usually up to 25mg/day	Tablet: 25mg, 50mg		Y
Hydrochlorothiazide (HCTZ) (Microzide)	Initial: 12.5-25mg PO QAM MDD: not established; usually up to 50mg/day (see comments)	Capsule: 12.5mg Tablet: 12.5mg, 25mg, 50mg		Y
Indapamide (Lozol)	Initial: 1.25mg PO QAM MDD: 5mg/day	Tablet: 1.25mg, 2.5mg		Y
Metolazone (Zaroxolyn)	Initial: 2.5-5mg PO QAM MDD: not established; usually up to 5mg/day	Tablet: 2.5mg, 5mg, 10mg		Y

References

1. Whelton PK, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ ASPC/ NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:e13–e115.
2. Wells BG, et al. Pharmacotherapy Handbook, 8th ed. New York: McGraw-Hill Education, 2012.
3. Alley WD, et al. Hypertensive Emergency. 2020 Nov 21. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 29261994.
4. Peixoto AJ. Acute severe hypertension. New England Journal of Medicine. 2019;381:1843-1852.
5. Scott IA, et al. Going beyond the guidelines in individualizing the use of antihypertensive drugs in older patients. Drugs & Aging. 2019;36:675-685.Lexi-Comp
6. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 2021;99(3S):S1–S87.
7. Corona A, et al. Fast Fact #408: Conservative management of patients with end stage renal disease. Palliative Care Network of Wisconsin Accessed online at: https://www.mypcnow.org/fast-fact/conservative-management-of-patients-with-end-stage-renal-disease/
8. Benetos A, et al. Treatment with multiple blood pressure medications, achieved blood pressure, and mortality in older nursing home residents: the PARTAGE study. JAMA Intern Med. 2015;175(6):989-995.
9. Tinetti ME, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA Intern Med. 2014;174(4):588-595.
10. Tinetti ME, et al. Health outcome priorities among competing cardiovascular, fall injury, and medication-related symptom outcomes. J Am Geriatr Soc. 2008;56(8):1409–16.
11. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.
12. Sheppard JP, et al. Effect of Antihypertensive Medication Reduction vs Usual Care on Short-term Blood Pressure Control in Patients With Hypertension Aged 80 Years and Older: The OPTIMISE Randomized Clinical Trial. 2020;323(20):2039–2051.
13. Elliott WJ, et al. Withdrawal syndromes with antihypertensive drug therapy. UpToDate (Accessed March 2021).
14. Hanlon JT, et al. Avoiding adverse drug withdrawal events when stopping unnecessary medications according to the STOPPFrail Criteria. Sr Care Pharm. 2021;36:136-141.
15. Podrid PJ. Major side effects of beta-blockers. UpToDate (Lit review current through Dec 2020, accessed Dec 2020).
16. IBM Micromedex Solutions. Truven Health Analytics, Inc; 2021.
17. Bloch MJ, et al. Major side effects and safety of calcium channel blockers. UpToDate (Lit review current through June 2021, accessed July 2021).
18. Clinical Resource, Bedtime Dosing of Blood Pressure Meds. Pharmacist's Letter/ Prescriber's Letter. January 2020.

Orthostatic Hypotension

DEFINITIONS

- **Hypotension** refers to low blood pressure (BP), generally defined as <90/60mmHg.
- **Orthostatic hypotension (OH),** also called postural hypotension, describes a temporary drop in blood pressure (≥20mmHg systolic or ≥10mmHg diastolic) within three minutes of standing up.[1]
- **Postprandial OH** describes a drop in blood pressure (>20mmHg systolic or to ≤90mmHg) within two hours of eating.[2]

ASSOCIATED SYMPTOMS

- Symptoms usually occur with sudden postural changes, but might also be associated with meals, exertion, and standing for prolonged periods.[3]
- Postprandial OH symptoms can occur when patients are in a seated position.[2]
- OH symptoms range in severity from mild to incapacitating.[1-3]
  - » Related to cerebral hypoperfusion: lightheadedness, dizziness, weakness, syncope, fatigue, difficulty thinking, "coat-hanger headache" (neck pain and headache localized at base of skull, back of neck, and shoulders)
  - » Related to autonomic compensation: palpitations, chest pain, lower back pain, nausea, tremor, cold extremities
  - » Older adults may present with atypical symptoms including speech disturbance, visual changes (blurred or tunnel vision), falls, confusion
- OH is a common cause of syncope (or transient loss of consciousness) in very old adults.[4]
- Symptomatic OH is associated with increased risk for falls and impaired quality of life.[3]
- Some patients with OH remain asymptomatic.[2,5]

CLINICAL INSIGHTS

- Chronic OH is more common in older patients, diabetics, neurogenic conditions (eg, Parkinson disease, dementia with Lewy bodies, multi-system atrophy, Alzheimer's disease) or fluid imbalance (eg, adrenal insufficiency).[1,2]
- Prolonged periods of immobility increase the incidence of OH in elderly patients.[1,5]
- Postprandial OH can aggravate existing OH.[1]
- OH is most commonly caused by drugs, particularly those that cause volume depletion or vasodilation **(Table 1)**. Elderly patients are more susceptible to the hypotensive effects of drugs.
- Straining during defecation or violent coughing can worsen OH.

TABLE 1. MEDICATIONS THAT CAN CAUSE ORTHOSTATIC HYPOTENSION[1,3,5-7]

RISK LEVEL	MEDICATIONS
Highest Risk	• Alpha-blockers (eg, terazosin, doxazosin) • Calcium channel blockers • Diuretics • Vasodilators (eg, hydralazine, NTG)
Lower Risk	• Antidepressants (eg, SSRIs, trazodone, TCAs, MAOIs) • Antihypertensives • Anti-Parkinson drugs (eg, levodopa, dopamine agonists) • Antipsychotics (due to alpha-blockade; most common with thioridazine, chlorpromazine, clozapine, iloperidone) • Beta-blockers • Muscle relaxers (esp. tizanidine, carisoprodol) • Opioids • PDE-5 inhibitors (eg, sildenafil, tadalafil) • Sedatives / hypnotics

Orthostatic Hypotension

TREATMENT

- The primary aim of OH treatment is to reduce symptoms rather than attain "normal" BP measurements.[8] Asymptomatic patients do not require treatment.
- Initial treatment generally involves non-pharmacologic measures.[1,2,5,8,9]
  - » Increased sodium/fluid intake
  - » Raise head of bed 30-45 degrees
  - » Abdominal binders
  - » Physical countermaneuvers (eg, standing up slowly, leg crossing, buttock clenching)
  - » Limit consumption of large, carbohydrate-rich meals to prevent postprandial OH
  - » Consume a small breakfast +/- one cup of coffee (or other caffeinated beverage), particularly when symptoms are more prevalent in the morning
- Fludrocortisone, midodrine, and droxidopa are the medications most commonly used to treat OH.
  - » BP tends to rise during the day, so larger morning doses and smaller evening doses of midodrine and droxidopa may be suitable.[2]
  - » Recommendations for midodrine and droxidopa are strongest for patients with neurogenic conditions.[2,5,8]
  - » If adequate titration of one agent is limited by side effects, combination therapy (ie, fludrocortisone plus midodrine or droxidopa) can be used to allow for reduced doses of each.[8,9]
- Other agents
  - » Adding erythropoietin, caffeine, pyridostigmine, or NSAIDs to traditional therapy may be useful.[8]
  - » Use of atomoxetine, desmopressin/DDAVP, metoclopramide, octreotide, and ergotamine for refractory symptoms has been reported, but is considered experimental.[5,8]
  - » In patients with autonomic failure, clonidine may paradoxically increase venous return and blood pressure.[2]
  - » Laxatives and antitussives can indirectly prevent symptoms when OH is constipation- or cough-induced.
- Pharmacologic treatment of OH commonly causes supine hypertension (supine HTN); patients who are primarily bedbound or lie down during the day are most susceptible.
  - » This may be offset by resting / sleeping in a seated position or with the head of the bed raised by 30-45 degrees.
  - » Take doses at least 4-5 hours before lying down to limit supine HTN.[8]
  - » Limit use of concomitant medications known to increase risk for supine HTN (eg, triptans, pseudoephedrine),[9] especially in patients at risk for developing a hypertensive crisis.

DEPRESCRIBING

- When possible, deprescribe drugs known to cause hypotension to facilitate deprescribing medications used to manage OH.
- Since OH primarily occurs when standing and subsides when lying down, deprescribing OH medications should be considered in patients who are non-ambulatory / bedbound.
- Deprescribe OH medications if persistent supine HTN or intolerable adverse effects occur.[10]
- Drug-specific adverse effects can warrant deprescribing.[10]
  - » Midodrine: bradycardia
  - » Fludrocortisone: edema (esp. in patients with heart failure (HF)), hyperglycemia (if affecting glycemic control in patients with brittle diabetes)

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CORTICOSTEROID[10]				
Fludrocortisone (Florinef)	Initial: 0.05-0.1mg PO QAM; may titrate by 0.1mg/week as tolerated MDD: 0.3mg/day	Tablet: 0.1mg	• First-line treatment • Increases sodium / water reabsorption; avoid in patient with edema and heart failure • May cause hypokalemia; potassium supplementation may be warranted[9] • May cause markedly elevated supine blood pressure; consider deprescribing in patients who are predominantly bedbound, unable to sit upright • Increased adverse effects and diminishing benefit with doses >0.2mg/day[8] • Steroid-induced diabetes uncommon at usual doses for OH, but hyperglycemic effect can compromise glycemic control in patients with brittle diabetes[2] • Onset of effect typically delayed by 5-10 days after starting therapy[8,9]	Y

Orthostatic Hypotension

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
VASOCONSTRICTORS[10]				
Midodrine (Amatine, ProAmatine)	Initial: 2.5mg PO TID (30 minutes before getting out of bed, before lunch, mid-afternoon) MDD: 30mg/day	Tablet: 2.5mg, 5mg, 10mg	**Vasocontrictors** • First-line treatment for neurogenic OH[2] • Titrate as tolerated to relieve symptoms • Administer at least 4-5 hours before lying down to limit supine HTN[8] • May cause markedly elevated supine blood pressure; consider deprescribing in patients who are predominantly bedbound, unable to sit upright • Do not combine with MAOIs • Expensive (droxidopa >> midodrine) • Can be combined with fludrocortisone[8] **Midodrine** • Alpha-agonist; does not cause CNS effects or increase heart rate[2,5] • Dose-related side effects include paresthesia, piloerection, scalp itching, urinary retention, headache, supine HTN[2] • Consider deprescribing if bradycardia occurs; more likely with doses >10mg or >30mg/day[10] • Contraindicated if acute renal failure, urinary retention, poorly controlled HTN • Paradoxical worsening of OH has been reported • Peak effect reached in about 1 hour; effects persist for 2-3 hours[9] **Droxidopa** • Norepinephrine precursor • May exacerbate ischemic heart disease, arrhythmia, HF • Common adverse effects include headache, dizziness, nausea • Risk for supine HTN may be lower than with midodrine[8] • Peak effect reached in about 3 hours[9]	Y
Droxidopa (Northera)	Initial: 100mg PO TID May titrate by 100mg TID every 24-48 hours as tolerated MDD: 1,800mg/day	Capsule: 100mg, 200mg, 300mg		N

Orthostatic Hypotension

References

1. Lee YL. Orthostatic hypotension in older people. J Am Assoc Nurse Pract. 2013;25:451-458.
2. Freeman R, et al. Orthostatic hypotension: JACC state-of-the-art review. JACC. 2018;72(11):1294-1309.
3. Kaufmann H. Mechanisms, causes, and evaluation of orthostatic hypotension. UpToDate (Literature review current through March 2021, accessed April 2021).
4. Zipes DP, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 11th ed. Philadelphia, PA: Elsevier; 2019.
5. Godbole GP, et al. Review of management strategies for orthostatic hypotension in older people. Journal of Pharmacy Practice and Research. 2018;48:483-491.
6. Jibson MD. First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects. UpToDate (Lit review current through March 2021, accessed April 2021)
7. Jibson MD. Second-generation antipsychotic medications: Pharmacology, administration, and side effects. UpToDate (Lit review current through March 2021, accessed April 2021)
8. Kaufmann H. Treatment of orthostatic and postprandial hypotension. UpToDate (Lit review current through March 2021, accessed April 2021)
9. Palma J, et al. Orthostatic hypotension in Parkinson disease. Clin Geriatr Med. 2020;36:53-67.
10. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.

Peripheral Artery Disease

DEFINITION[1,2]

Peripheral artery disease (PAD) is compromised / obstructed blood flow in the extremities that can lead to ischemic limb pain, most commonly in the lower leg(s).

ASSOCIATED SYMPTOMS

- Up to 50% of patients ≥50 years old as well as most cases of upper extremity PAD are asymptomatic, but lower extremity pain is common.[2,3]
- Symptoms range in severity from mild discomfort (eg, pain, aching, fatigue) to severe, debilitating pain in the buttocks, thighs, calves, or feet.[1,2]
- Ischemic limb pain usually manifests as intermittent claudication or chronic limb-threatening ischemia (CLTI) in the lower extremities.[4]
- Intermittent claudication (IC) is reproducible pain or discomfort in the lower extremities that is initially precipitated by exertion (including walking) and resolved with rest (usually after several minutes).[1,2]
  - » Claudication may be unilateral or bilateral.
  - » Over time, pain can intensify and occur at rest or with small changes in positioning.
- CLTI is a severe form of limb ischemia resulting in pain, gangrene, or non-healing ulcers lasting >2 weeks.[1,2,4]
  - » Symptoms include severe pain, sensitivity, or paresthesia in the forefoot or toes of the affected extremity; they occur at rest and worsen with leg elevation.[1]
  - » Ulcers vary in size and have a pale base with irregular borders; they typically develop on the tips of toes, on the heels, or at other sites of pressure.[1]

CLINICAL INSIGHTS

- In the hospice setting, the goals of therapy are to minimize pain and other claudication symptoms and preserve ambulation.[1] Traditional aims of therapy include modifying risk factors (eg, diabetes, hypertension) to reduce risk for cardiovascular events and prevent further limb damage; however, it is questionable if these treatments are beneficial in terminally ill patients.
- Revascularization procedures can restore perfusion, limit tissue loss, and improve pain in severe PAD affecting both upper and lower extremities. In the most severe cases (ie, CLTI), amputation may be warranted.[5]
  - » Hospice patients are inherently poor candidates for these interventions; instead, palliative interventions including pain management and wound care are preferred.[6]
- Antibiotic treatment with broad-spectrum agents may be considered in cases of infection; however, it is uncertain what palliative benefit is provided without revascularization and/or debridement.[6]
- Smoking cessation reduces the risk for developing symptomatic PAD or progressing to limb-threatening ischemia; however, successfully quitting with treatment typically takes several months so is probably of limited utility in the hospice setting.[1,7]
- Cilostazol or pentoxifylline may improve ambulation and/or prevent pain in patients with IC.[1]
  - » Symptom improvement is generally greater with cilostazol.[7]
  - » Both have a slow time to onset (minimum of 2 to 4 weeks; up to 12 weeks with cilostazol)[8]; they should not be initiated in the hospice setting if their time to onset exceeds life expectancy.
  - » If IC symptoms occur at rest or with repositioning, continued use in hospice patients is reasonable; but, if symptoms only occur with ambulation, they can be discontinued once ambulation is lost.

- Ischemic limb pain should be managed with analgesics and adjuvants.
  - » Incident pain can be so sudden and severe that analgesic agents with short time to onset are preferred.
    - ° Patient-controlled analgesia (PCA) devices may be necessary.[9]
  - » Topical agents may also be effective such as custom compounds including morphine, clonidine, nitrates, or vasodilators.[4,9]
  - » Other interventions for consideration include opioids, gabapentin, and ketamine or lidocaine infusions.[4,9]
- CLTI pain / discomfort can be relieved by sitting on the edge of the bed and letting the legs hang / dangle or by walking around the room due to the gravitational effects of limb dependence on perfusion.[1,2] The patient's bed should be positioned so that their feet rest below chest level when lying down.[1]
- Antiplatelet medications produce negligible improvement in IC symptoms and their primary role in PAD treatment is for prevention of coronary heart disease and stroke.[7]
- Medications with uncertain benefit for symptomatic improvement in PAD include anticoagulants, serotonin antagonists, alpha-blockers, l-arginine, carnitine derivatives, vasodilating prostaglandins, antibiotics, statins, and hormone replacement therapies.[1,7]
- Anticoagulants may be used in some cases of limb ischemia to limit the proliferation of thrombosis contributing to ischemic limb pain.[6]

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DRUGS FOR INTERMITTENT CLAUDICATION				
Cilostazol[7,8] (Pletal)	Initial: 100mg PO BID Reduce dose to 50mg BID if combined with CYP3A4 / CYP2C19 inhibitors MDD: same as initial dosing	Tablet: 50mg, 100mg	• First-line for improving ambulation and preventing pain[1,5] • Antiplatelet, PDE-3 inhibitor • 2 to 12 weeks of treatment typically required for therapeutic effects • Discontinue if symptoms not improved after 3 months of treatment • Use cautiously in patients with increased risk for bleeding / falls or who take other medications associated with bleeding (eg, NSAIDs, anticoagulants, antiplatelets) • Contraindicated if heart failure • May exacerbate angina/ischemic heart disease • Caution in severe renal impairment • Common side effects include headache, diarrhea, nausea, back pain, infection, rhinitis, palpitations, peripheral edema, dizziness • Major CYP2C19, CYP3A4 substrate; CYP3A4 inhibitor • Grapefruit juice, high-fat meals may increase drug levels	Y
Pentoxifylline[7,8] (Trental)	Initial: 400mg PO TID MDD: same as initial dosing	Tablet (ER): 400mg	• Minimal improvements in walking distance compared to exercise or treatment with cilostazol • Delayed time to onset (2 to 4 weeks) • Contraindicated if recent retinal / cerebral hemorrhage • Requires renal dose adjustments • Caution in hepatic impairment • Use cautiously in patients with increased risk for bleeding / falls or who take other medications associated with bleeding (eg, NSAIDs, anticoagulants, antiplatelets)	N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIPLATELETS FOR PREVENTION				
Aspirin (ASA)[8,10] (Bayer, St. Joseph Adult Aspirin)	Initial: 81mg PO QD MDD: same as initial dosing	Chewable tablet: 81mg Tablet (EC)*: 81mg Numerous other forms exist, however 81mg is the recommended dose for this indication	• Non-palliative • Increased risk for major bleeding and uncertain benefit when used for primary prevention in patients ≥70 years old • Use cautiously in patients with increased risk for bleeding / falls or who take other medications associated with bleeding (eg, NSAIDs, anticoagulants, antiplatelets) • Avoid in severe liver impairment • Upper GI events (incl. symptomatic ulcers) increased 2-4x, even when used at low, cardioprotective doses; avoid in active peptic ulcer disease; consider adding gastroprotection (eg, PPI) if combined with NSAIDs	Y/N*
Clopidogrel[8,10] (Plavix)	Initial: 75mg PO QD MDD: same as initial dosing	Tablet: 75mg	• Non-palliative • May be used in place of ASA • Contraindicated if active bleeding • Use cautiously in patients with increased risk for bleeding / falls or who take other medications associated with bleeding (eg, NSAIDs, anticoagulants, antiplatelets) • Pro-drug, requires conversion to active metabolite by CYP2C19 enzyme; alternate therapy may be warranted in patients taking CYP2C19 inhibitors / inducers • Grapefruit juice may reduce serum levels, efficacy	Y

References

1. Zipes DP, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 11th ed. Philadelphia, PA: Elsevier; 2019.
2. Neschis DG, et al. Clinical features and diagnosis of lower extremity peripheral artery disease. UpToDate. (Lit review current through July 2021, accessed August 2021).
3. Barshes NR. Overview of upper extremity peripheral artery disease. UpToDate. (Lit review current through July 2021, accessed August 2021).
4. Pickmans L, et al. Fast Fact #352: Management of ischemic limb pain. Accessed online at: https://www.mypcnow.org/fast-fact/management-of-ischemic-limb-pain/
5. Berger JS. Overview of lower extremity peripheral artery disease. UpToDate. (Lit review current through Feb 2020, accessed March 2020).
6. Neschis DG, et al. Management of chronic limb-threatening ischemia. UpToDate. (Lit review current through July 2021, accessed August 2021).
7. Davies MG, et al. Management of claudication due to peripheral artery disease. UpToDate (Lit review current through Feb 2020, accessed Feb 2020)
8. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.
9. Woelk CJ. Management of critical limb ischemia. Canadian Family Physician. 2012;58(9):960-963.
10. Alonso-Coello P, et al. Antithrombotic Therapy in Peripheral Artery Disease - Antithrombotic therapy and prevention of thrombosis, 9th ed; ACCP Guidelines. CHEST. 2012;141(2)(Suppl):e669S-e690S.

Pulmonary Arterial Hypertension

DEFINITIONS[1,2]

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by elevated blood pressure in the pulmonary arteries. PAH is caused by narrow, thick, or stiff arteries restricting blood flow in the lungs; this ultimately leads to right-sided heart failure.

There are different types of PAH, commonly categorized by cause or association with other conditions:

- **Idiopathic PAH:** unknown cause
- **Heritable PAH:** associated with inherited genetic defects
- **Drug or toxin-induced PAH:** associated with the use of drugs or toxins that are known or potential risk factors for developing PAH; this is most commonly associated with methamphetamines, certain appetite suppressants (eg, fenfluramine), and dasatinib
- **Associated PAH:** related to a variety of systemic disorders including connective tissue diseases (eg, scleroderma, rheumatoid arthritis, lupus), HIV, portal hypertension, certain congenital heart diseases, and schistosomiasis

Disambiguation: Pulmonary hypertension (PH) is classified into five different groups, generally defined by their underlying causes (**Table 1**). This monograph describes PAH (Group 1 pulmonary hypertension).

TABLE 1. PULMONARY HYPERTENSION (PH) CLASSIFICATION[2]

GROUP	CLASSIFICATION
Group 1	Pulmonary arterial hypertension
Group 2	PH due to left heart disease
Group 3	PH due to chronic lung disease and/or hypoxemia
Group 4	PH due to pulmonary artery obstructions
Group 5	PH due to unclear or multifactorial mechanisms

ASSOCIATED SYMPTOMS[1,3]

- Dyspnea, syncope, fatigue, chest pain, palpitations, peripheral edema
- Cough, hemoptysis, and hoarseness have been reported but are uncommon.
- In advanced stages of PAH, symptoms including pain, anxiety, depression, and existential distress are common.

CLINICAL INSIGHTS

- When possible, consultation with a clinician who has expertise in treating PAH is recommended prior to medication changes.
- Disease-targeted therapy is an evidence-based standard of care involving medications directed at PAH itself, rather than an underlying cause.
  - » Associated with improved symptoms, function, and quality of life (**Table 2**).[1]
  - » Aimed at modulating prostacyclin, endothelin, and nitric oxide-related pathways
  - » Promotes vasodilation in pulmonary arterioles and has antiproliferative effects on smooth muscle cells and fibroblasts in pulmonary arteries
  - » In most cases, one or more disease-targeted therapies are necessary.
- Hospices who admit patients with PAH should anticipate that symptom management typically requires expensive disease-targeted therapies.
- Current guidelines suggest that anticoagulants may improve survival in some types of PAH, but symptomatic benefit should not be expected.[1] The decision to continue anticoagulants should be individualized.
- Prostacyclins should be continued for as long as tolerated; even temporary discontinuation can be fatal.[1]

Pulmonary Arterial Hypertension

TABLE 2: PALLIATIVE MEDICATIONS FOR PULMONARY ARTERIAL HYPERTENSION BASED ON EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS AND CONSENSUS GUIDELINES[1,4,5]

Medications	Palliative Improvements			
	Dyspnea	Exercise capacity*	Functional class**	Quality of life
Calcium channel blockers (CCBs)				
amlodipine, diltiazem†, nifedipine			X	
Prostacyclins				
epoprostenol (IV)	X	X	X	X
iloprost (inhaled)	X	X	X	X
selexipag (PO)		X		
treprostinil (CIVI)		X		
treprostinil (CSCI)	X	X		
treprostinil (inhaled)		X‡		
Endothelin receptor antagonists (ERA)				
ambrisentan	X	X		
bosentan	X	X	X	
macitentan	X	X	X	X
PDE5 inhibitors (PDE5I)				
sildenafil		X	X	X
tadalafil		X	X	X
Guanylate cyclase stimulant				
riociguat	X	X	X	X

IV = intravenous, CSCI = continuous subcutaneous infusion, CIVI = continuous intravenous infusion, PO = oral

†verapamil should be avoided due to negative inotropic effects

‡when added to ERA or PDE5I

*measured by 6-minute walk test (6MWT), a proxy for physical capability

**despite treatment, eventual deterioration is common

CALCIUM CHANNEL BLOCKERS (CCBs)

- The use of CCBs in PAH is generally limited to a small subset of patients who have demonstrated "vasoreactivity" in a monitored setting. For patients not already receiving CCBs, they should not be considered as therapeutic alternatives to other disease-targeted therapies.
- Patients with PAH who are taking CCBs when admitted to hospice are likely to be long-term responders and these medications should be continued for as long as the patient can tolerate them. Premature withdrawal may precipitate rapid deterioration in clinical status.[1]
- Extended-release (ER) nifedipine, ER diltiazem, and amlodipine are most commonly used.[6]
- Verapamil is typically avoided due to its negative inotropic effects.[5]

VOLUME OVERLOAD

- Fluid retention is extremely common in advanced PAH; diuretic combinations (eg, furosemide + metolazone + spironoloactone) are often required to regulate fluid volume and manage associated symptoms.[1]
- Gut edema can impair absorption of oral medications; parenteral diuretics (eg, IV/SQ furosemide) may be necessary.

Pulmonary Arterial Hypertension

THERAPEUTIC SUBSTITUTION

- Patients with more severe disease, worse functional status, and higher doses of medications are less likely to successfully transition between therapies.[7]
- CCBs are not appropriate substitutes for other disease-targeted therapies.
- Strategies for switching from parenteral to oral prostacyclins have been described, but the higher cost of oral therapies may be a barrier to their initiation once admitted to hospice and parenteral prostacyclins remain a standard of care in patients with more advanced disease.[8,9]
- Transition from SQ treprostinil to PO sildenafil was safely achieved in patients who wanted to discontinue the use of painful injections (**Figure 1**).[10]

FIGURE 1. EXAMPLE PROTOCOL FOR SWITCHING FROM SQ TREPROSTINIL TO PO SILDENAFIL*[10]

Step 1:	Gradually reduce treprostinil to 50% of maintenance dose by tapering at a rate of 2.5ng/kg/min/week
Step 2:	• Start sildenafil • Taper treprostonil over the course of 4 weeks and discontinue

*While a majority of patients experienced improvements in functional class and quality of life following the switch, some experienced acute deterioration with treprostinil withdrawal. Most patients enrolled in the study reported NYHA class III symptoms at baseline; it is unknown whether patients with more severe symptoms (ie, NYHA class IV) would similarly tolerate such a switch.

DEPRESCRIBING PARENTERAL PROSTACYCLINS

- Abrupt discontinuation can lead to acute clinical deterioration, worsening symptoms, and death.[11]
- Opioids and benzodiazepines can be used to manage associated symptoms; premedication prior to withdrawal is recommended.[11]
- Ideally, prostacyclin withdrawal should take place in the inpatient setting due to staff familiarity with aggressive symptom management. In-home withdrawal may be considered, but requires physician supervision.[11]
- Gradually reduce doses by 20 to 25% (epoprostenol: every 25-30 minutes; treprostinil: every 4-6 hours).[11]
  - » If new or worsening symptoms occur, hold the taper until symptoms are adequately managed and then resume taper in smaller increments at a slower rate.
  - » The rate of withdrawal may be cautiously increased in unresponsive patients who appear to be tolerating the taper with minimal symptom burden.

OTHER DEPRESCRIBING GUIDANCE FOR SELECT DISEASE-TARGETED THERAPIES

- ERAs: severe peripheral edema may warrant discontinuation[1]
- Bosentan: Reduce dose to 62.5mg twice daily for 3-7 days, then discontinue[9]
- Treprostinil (Oral): Reduce the total daily dose by 0.5-1mg per day until discontinued[9]
- Selexipag: treatment interruption is well tolerated for up to 14 days.[12] The effects of therapy interruption beyond this period are not known.

Pulmonary Arterial Hypertension

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CALCIUM CHANNEL BLOCKERS (CCBs)[4,9,13]				
Amlodipine (Norvasc, Katerzia)	Initial: 2.5mg PO QD MDD: 20mg/day	Oral Suspension: 1mg/ml Tablet: 2.5mg, 5mg, 10mg	**Calcium Channel Blockers** • Reserved for patients who demonstrate vasoreactivity in a monitored setting; do not substitute for other disease-targeted therapies • Headache is a common adverse effect • Geriatric patients more susceptible to hypotension, constipation • Dose-dependent peripheral edema is common • Major CYP3A4 substrates; many drug interactions • Grapefruit juice may increase drug levels; avoid if taking nifedipine • Discontinuation may lead to clinical decline **Amlodipine, Diltiazem, Nifedipine** • Caution in hepatic impairment **Amlodipine & Nifedipine** • May cause dizziness, light-headedness, flushing **Amlodipine** • Oral suspension is expensive **Diltiazem** • *Most ER formulations should not be crushed or opened (Taztia XT and Tiazac are exceptions) • Caution in renal impairment • Moderate CYP3A4 inhibitor **Nifedipine** • IR formulation not recommend due to risk for severe hypotension	Y
Diltiazem (Cardizem CD/LA, Cartia XT)	Initial (ER, 24-hr): 120mg PO QD MDD: 720mg/day	Capsule (ER, 12-hr)*: 60mg, 90mg, 120mg Capsule (ER, 24-hr)*: 120mg, 180mg, 240mg, 300mg, 360mg, 420mg Tablet: 30mg, 60mg, 90mg, 120mg Tablet (ER, 24-hr)*: 120mg, 180mg, 240mg, 300mg, 360mg, 420mg		Y/N*
Nifedipine (Adalat CC, Nifediac CC, Nifedical XL, Procardia XL)	Initial (ER): 30-60mg PO QD MDD: 240mg/day	Tablet (ER): 30mg, 60mg, 90mg		N

Pulmonary Arterial Hypertension

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ENDOTHELIN RECEPTOR ANTAGONISTS (ERAs) [4,9]				
Ambrisentan (Letairis)	Initial: 5mg PO QD MDD: 10mg/day	Tablet: 5mg, 10mg	**Endothelin Receptor Antagonists** • Improve dyspnea, exercise capacity, functional class, and/or quality of life (**Table 2**) • REMS program enrollment required for prescribers, pharmacies, patients; dispensing restricted to specialty pharmacies • Common side effects are peripheral edema and headache • Severe cases of peripheral edema warrant discontinuation; use caution in HF[1] • Expensive **Ambrisentan & Bosentan** • Avoid in moderate or severe hepatic impairment **Ambrisentan** • Peripheral edema more common in elderly or when combined with tadalafil (frequently used in combination) • Contraindicated in idiopathic pulmonary fibrosis **Bosentan** • Moderate CYP3A4 inducer • REMS: monthly liver function tests required **Macitentan** • Nasal congestion and upper respiratory infections common[1] • Major CYP3A4 substrate; many drug interactions	N
Bosentan (Tracleer)	Initial: 62.5mg PO BID MDD (<40kg): 125mg/day MDD (≥40kg): 250mg/day	Solutab: 32mg Tablet: 62.5mg, 125mg		Y
Macitentan (Opsumit)	Initial: 10mg PO QD MDD: 10mg/day	Tablet: 10mg		N

Pulmonary Arterial Hypertension

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
GUANYLATE CYCLASE STIMULANT[9]				
Riociguat (Adempas)	Initial: 0.5-1mg PO TID MDD: 7.5mg/day; higher doses may be needed in smokers (due to increased drug clearance)	Tablet: 0.5mg, 1mg, 1.5mg, 2mg, 2.5mg	• Improves exercise capacity, functional class, and/or quality of life (**Table 2**) • Promotes vasodilation • REMS program enrollment required for prescribers, pharmacies, and female patients; dispensing restricted to specialty pharmacies • May cause severe hypotension » Contraindicated with PDE inhibitors and nitrates • Significant interactions with protease inhibitors, ketoconazole, and itraconazole • Adverse effects include hypotension, headache, dizziness, dyspepsia, nausea, vomiting, diarrhea, serious bleeding • If hypotensive effects are not tolerated, reduce by 0.5mg per dose • Avoid in severe renal or hepatic impairment • Concentrations are 50-60% lower in smokers; consider dose reduction if patient stops smoking • CYP3A4, BCRP, P-glycoprotein substrate	Y

Pulmonary Arterial Hypertension

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
PHOSPHODIESTERASE-5 INHIBITORS (PDE5Is)[9]				
Sildenafil (Revatio)	Initial (PO): 20mg TID (give doses 4-6 hours apart) Initial (IV): 10mg TID MDD (PO): 240mg/day MDD (IV): Not established	Oral suspension: 10mg/ml Solution for injection: 10mg/12.5ml Tablet: 20mg	**PDE-5 Inhibitors** • Improve exercise capacity, functional class, and/or quality of life (**Table 2**) • Promote vasodilation • Do not discontinue abruptly • Adverse effects include flushing, headache, dyspepsia, visual disturbance, myalgia, and epistaxis • May cause hearing / vision impairment • May cause severe hypotension » Contraindicated with riociguat and nitrates » Use alpha-blockers with caution • If nitrates are medically necessary, separate doses (sildenafil: ≥24 hours, tadalafil: ≥48 hours); administration in monitored setting recommended • Major CYP3A4 substrate; many drug interactions • Grapefruit juice may increase drug levels • It is reasonable to substitute strengths of generic Viagra or Cialis for cost avoidance **Sildenafil** • 10mg IV ≈ 20mg PO[14] • Caution in sickle-cell anemia **Tadalafil** • Requires renal dose adjustments • Avoid in severe renal / hepatic impairment • Frequently used in combination with ambrisentan for synergistic effects	Y
Tadalafil (Adcirca)	Initial: 40mg PO QD MDD: 40mg/day	Tablet: 20mg		Y

Pulmonary Arterial Hypertension

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
PROSTACYCLINS[9]				
Epoprostenol (Flolan, Veletri)	Initial (CIVI): 2ng/kg/min MDD: not established; usual maintenance dose (monotherapy): 25-40ng/kg/min	Solution for injection: 0.5mg, 1.5mg	**Prostacyclins** • Improve dyspnea, exercise capacity, functional class, and/or quality of life (**Table 2**) • Promote vasodilation and inhibit platelet aggregation • Generally reserved for patients with refractory symptoms and more advanced disease[4] • Parenteral agents preferred for more severe disease • Common dose-related adverse effects include hypotension, headache, diarrhea, nausea, flushing, joint / muscle aches, and jaw pain • Dispensing restricted to specialty pharmacies • Expensive **Epoprostenol, Iloprost, Treprostinil** • Caution if risk for bleeding • Abrupt discontinuation / dose reduction can lead to clinical deterioration or death[1] **Epoprostenol** • Prostacyclin of choice for more severe symptoms • Infused through central venous catheter • Very short half-life (~6 minutes); immediate access to backup medication and supplies recommended to prevent treatment interruption, worsening symptoms • Monitor HR/BP for several hours after dose increases to ensure tolerance • Stability dependent on storage temperature, diluent, concentration *(Continued on next page)*	-
Iloprost (Ventavis)	Initial (inhalation): 2.5mcg/dose six to nine times a day (≥2 hour intervals, while awake) MDD: 45mcg/day	Solution for nebulization: 10mcg/ml, 20mcg/ml		-
Selexipag (Uptravi)	Initial: 200mcg PO BID MDD: 3,200mcg/day	Tablet: 200mcg, 400mcg, 600mcg, 800mcg, 1,000mcg, 1,200mcg, 1,400mcg, 1,600mcg		N
Treprostinil (Orenitram, Remodulin, Tyvaso)	Initial (PO): 0.125mg Q8 hours or 0.25mg Q12 hours Initial (inhalation): 18mcg (3 inhalations) nebulized QID; administered Q4 hours while awake Initial (CIVI/CSCI): 0.625-1.25ng/kg/minute MDD (PO): as tolerated; target doses up to 24mg/day reported MDD (inhalation): as tolerated; target dose of 36 inhalations (216mcg)/day reported MDD (CIVI/CSCI): not established; target dose is generally 40-80ng/kg/minute	Solution for injection: 1mg/ml, 2.5mg/ml, 5mg/ml, 10mg/ml Solution for nebulization: 0.6mg/ml Tablet (ER): 0.125mg, 0.25mg, 1mg, 2.5mg, 5mg		N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
PROSTACYCLINS[9] (CONTINUED)				
			Iloprost • For use with I-neb AAD System • If moderate to severe hepatic impairment, extended dosing intervals (eg, Q3-4 hours) may be needed based on response • May cause bronchospasm • Avoid if hypotension **Selexipag** • Indicated in earlier stages of PAH to delay disease progression; does not improve dyspnea • Requires hepatic dose adjustment; avoid in severe hepatic impairment • Take with food to minimize GI upset • Major CYP2C8 substrate **Treprostinil** • Requires dose adjustment in hepatic impairment; avoid in moderate or severe hepatic impairment • Oral: Q8 hour dosing may may be more tolerable than Q12 hour dosing • Inhalation: for use with Tyvaso Inhalation System	

References

1. Christiansen DC, et al. Pulmonary arterial hypertension: A palliative medicine review of the disease, its therapies, and drug interactions. Journal of Pain and Symptom Management. 2020;59(4):932-943.
2. Simonneau G, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. European Respiratory Journal. 2019;53(1).
3. Rubin LJ, et al. Clinical features and diagnosis of pulmonary hypertension of unclear etiology in adults. UpToDate (Accessed April 2021).
4. Klinger JR, et al. Therapy for pulmonary arterial hypertension in adults: Update of the CHEST guideline and expert panel report. CHEST. 2019;155(3):565-586.
5. McLaughlin VV, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573-1619.
6. Hopkins W, et al. Treatment of pulmonary arterial hypertension (group 1) in adults: Pulmonary hypertension-specific therapy. UpToDate (Accessed March 2021).
7. Sofer A, et al. A systematic review of transition studies of pulmonary arterial hypertension specific medications. Pulmonary Circulation. 2017;7(2):326–338.
8. Sargent T, et al. Transitions between infused and oral prostacyclin pathway agents in pulmonary arterial hypertension. Pulmonary Circulation. 2020;10(3):1-7.
9. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.
10. Keogh AM, et al. Safety and efficacy of transition from subcutaneous treprostinil to oral sildenafil in patients with pulmonary arterial hypertension. J Heart Lung Transplant 2007;26:1079–83.
11. Bartlett C, et al. Fast Fact #264: Prostacyclin withdrawal in pulmonary hypertension. Accessed online at: https://www.mypcnow.org/fast-fact/prostacyclin-withdrawal-in-pulmonary-hypertension/
12. Preston IR, et al. Temporary treatment interruptions with oral selexipag in pulmonary arterial hypertension: Insights from the Prostacyclin (PGI) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) study. J Heart Lung Transplant. 2018;37(3):401-408.
13. Galie N, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal. 2016;37:67-119.
14. Meds for pulmonary arterial hypertension. Pharmacist's Letter/Prescriber's Letter. March 2017.

Stroke

DEFINITION[1]

Stroke is an acute loss of neurologic function caused by interrupted blood flow to the brain.

- **Ischemic stroke**, the most common type of stroke, occurs when blood flow is interrupted by a blockage, such as a clot.
- **Hemorrhagic stroke** occurs when an artery in the brain ruptures or leaks, leading to increased pressure in the brain that ultimately damages brain cells.
- **Transient ischemic attack (TIA)**, also called "mini-stroke," describes a temporary interruption of blood flow to the brain, generally not lasting more than 5 minutes. It is typically a warning sign of a future stroke.

SYMPTOMS

ACUTE / INITIAL PRESENTATION[2-4]

- Ischemic stroke
  - » Facial droop, unilateral numbness or weakness of face / arm / leg, confusion, aphasia, impaired vision in one or both eyes, dizziness, ataxia, difficulty walking, headache, bowel / bladder incontinence, fever
- Hemorrhagic stroke
  - » Headache, vomiting, fever, seizures, dizziness, respiratory depression, focal neurological deficits (eg, weakness, paralysis), impaired consciousness, coma
- TIA
  - » Typically presents as transient, focal neurologic symptoms which can be attributed to a particular section of the brain dependent on the affected arteries.
    - ° Aphasia, slurred speech, hemiparesis and/or hemisensory loss

POST-STROKE SEQUELAE / COMPLICATIONS[5]

- Anxiety
- Cognitive impairment
- Communication difficulty
- Contractures
- Depression
- Emotional lability
- Dysphagia
- Falls / fear of falling
- Fatigue
- Fracture
- Headache
- Incontinence (bowel / bladder)
- Mobility impairment
- Pain; See **Table 1** for descriptions of select post-stroke pain syndromes
- Pressure ulcers, skin breakdown
- Seizure
- Spasticity
- Thromboembolism

CLINICAL INSIGHTS

- Stroke is a leading cause of severe, long-term disability.[1]
- Motor strength, limb mobility, cognition, communication, incontinence, pain, dysphagia, sensory impairment, spasticity, and balance tend to improve rapidly following stroke, but maximum restoration of function follows a prolonged course and recovery may fluctuate over time.[5]

STROKE PREVENTION

- Various tools exist to estimate the risk of future cardiovascular events and guide preventative treatment decisions (eg, 10-year ASCVD risk estimate, Framingham CVD risk score, Reynolds risk score).
  - » None have been validated in the hospice population.
- For patients >75 years old, guidelines recommend having discussions about the potential benefits of preventative treatment with consideration for comorbidities and life expectancy.[10] A similar approach should be taken for any hospice patient.

TABLE 1. CLINICAL PRESENTATION OF SELECT POST-STROKE PAIN SYNDROMES[6-9]

CLASSIFICATION	POST-STROKE ONSET	LOCATION	PAIN FEATURES / DESCRIPTORS	OTHER FEATURES
Central Post-Stroke Pain (CPSP)	Immediate to years; usually within a few months of stroke	Poorly localized; ranging from a small area (eg, left hand) to a large area (eg, entire left side of body)	• Spontaneous or evoked • No relation to movement, inflammation, or local tissue damage • All pain descriptors apply; incl. burning, aching, freezing, pricking, pins and needle, electric shocks, stinging, squeezing, lacerating, shooting	• Sensory abnormalities: hyperalgesia and abnormal thermal sensation (allodynia or dysesthesia in response to touch or cold)
Complex Regional Pain Syndrome (CRPS), aka 'shoulder-hand syndrome'	4-6 weeks	Affects a region of the body (usually upper limbs); may spread to adjacent areas or other limbs	• Spontaneous or evoked • Neuropathic; described as burning, stinging, tearing • Superficial or deep	• Sensory abnormalities (eg, allodynia, hyperalgesia, hypesthesia) usually presenting in extremity of affected limb in a stocking / glove pattern • Edema • Sweating • Changes in skin color / temperature • Skin / hair / nail changes • Reduced mobility of affected shoulder
Hemiplegic Shoulder Pain (HSP)	2 weeks to 3 months	Shoulder / upper extremity	• Nociceptive • Pain may be associated with spasticity	• Reduced mobility of affected shoulder (may overlap with CRPS) • Tenderness • Edema • Pain with movement • Decreased coordination • Positive Neer sign (pain with placement of fully pronated arm in forced flexion)

- Recurrent strokes are typically more disabling than the first stroke.[11] As such, hospice clinicians may choose to continue preventative therapies following stroke; they should only do so after carefully considering end-of-life treatment goals and weighing out the harms of continued treatment, which often involves the use of multiple medications.
- Aspirin (ASA) for primary prevention of ischemic stroke is controversial; although it reduces the risk for atherothrombosis through irreversible platelet inhibition, it also increases the risk for bleeding (esp. in the GI tract).
  - » It is difficult to balance the benefits and harms of prophylactic therapy in patients without prior ASCVD because, compared to patients with a prior history, they are inherently less likely to have future events.[10]
  - » ASA for primary prevention is not recommended in patients >70 years old; the risk for major bleeding from ASA is significantly increased in older patients.[10]
  - » ASA for primary prevention is not recommended in any patient at increased risk of bleeding.[10,12] Risk factors for bleeding include previous bleed in GI tract or from other sites, peptic ulcer disease, thrombocytopenia, coagulopathy, CKD, and concomitant use of other medications that increase bleeding risk (eg, NSAIDs, steroids, anticoagulants).
- Antithrombotic monotherapy (eg, anticoagulant, antiplatelet) is an established treatment for secondary prevention and is started for most patients following ischemic stroke.[13]
  - » Although guidelines recommend short-term dual antiplatelet therapy (DAPT) for certain patients

following stroke, it should be discontinued for most patients at 21 days post-stroke due to diminishing benefits beyond this period and increased bleeding risk.[5,13]
  - » Extended duration combination therapy is not typically indicated for stroke prevention alone, but may be considered for patients with other compelling indications (eg, DAPT following MI or stent placement).
  - » Anticoagulants are used preferentially for patients with atrial fibrillation, a common and high-risk condition for ischemic stroke (See **Atrial Fibrillation / Atrial Flutter** monograph).[13]

- Patients with strokes attributed to cancer-related hypercoagulability may have a higher risk for bleeding related to the use of anticoagulants; the benefits of anticoagulation in this population are not well-established.[13]

DEPRESCRIBING

- Primary and secondary prevention strategies involve aggressive treatment of chronic conditions that are risk factors for future stroke; however, such approaches are largely non-palliative and in many cases the drugs used to treat them are appropriate deprescribing targets due to the burdens and risks associated with their use (eg, polypharmacy, adverse effects). Dysphagia that prevents swallowing oral dosage forms should prompt medication discontinuation, particularly for drugs that do not provide a palliative benefit.
- Antihypertensives
  - » Based on studies of otherwise healthy individuals, blood pressure lowering affords significant relative risk reduction, albeit, with a modest absolute risk reduction.[14]
- Antiplatelets & Anticoagulants
  - » Deprescribe in patients experiencing bleeding.
  - » Consider deprescribing antiplatelets in patients with a prognosis <1 week, since inhibited platelets continued to circulate in the blood for approximately 10 days and strokes are less likely to occur within this period.[15]
  - » If antiplatelets or anticoagulants are deprescribed, gastroprotective drugs (eg, PPIs, H2RAs) may also be able to be deprescribed.
- Lipid-lowering drugs
  - » Deprescribing drugs used to treat hyperlipidemia (eg, statins) is a commonly accepted practice in patients with terminal illness.
  - » A study of statin discontinuation in hospice patients found that it improved quality of life and did not affect survival.[16]
- See **Atrial Fibrillation / Atrial Flutter** and **Hypertension** monographs for additional clinical insights on deprescribing.

POST-STROKE SEQUELAE

- Botulinum toxin injections (eg, Botox®) have been studied for a variety of post-stroke conditions including hemiplegic shoulder pain, headache, bladder dysfunction, and spasticity / contractures.[8,17-19]
  - » May take up to 2 weeks for initial improvement in symptoms.[20]
  - » Despite relatively high cost (AWP ~$750 / 100 units), they often provide sustained relief.[20]
- Central Post-Stroke Pain (CPSP)
  - » Amitriptyline and lamotrigine are often cited as first-line treatments; this is largely based on single studies of each.[19,21,22]
  - » The use of anticonvulsants to treat CPSP is based on the assumption that treatment response is consistent across chronic neuropathic pain conditions (see **Neuropathic Pain** monograph).[19,21]
  - » IV ketamine, lidocaine, and propofol have been used in refractory cases.[8,22]
- Complex regional pain syndrome (CRPS)
  - » Initial management generally involves NSAIDs, adjuncts for neuropathic pain (see **Neuropathic Pain** monograph), and/or lidocaine cream; combination therapy may be necessary.[23]
  - » Corticosteroids (oral), bisphosphonates, calcitonin, prazosin, ketamine, and opioids have also been used.[23]
- Hemiplegic shoulder pain (HSP)
  - » Treatment generally involves simple analgesics (APAP, NSAIDs); antispasmodics are recommended for patients with spasticity (see **Nociceptive / Tissue Pain** and **Muscle Spasm / Spasticity** monographs).[8]

» Corticosteroid injections (usually triamcinolone) are commonly used to treat shoulder pain and have been associated with short-term reductions in pain.[19]

- Pseudobulbar affect (PBA) / Emotional Lability
  - » Disturbances of emotional behavior are common after stroke and may present as PBA — unprovoked, exaggerated laughing or crying inconsistent with the patient's current emotional state.
  - » Dextromethorphan / quinidine can improve PBA symptoms and reduce episode frequency.[24,25] It can be compounded into an oral suspension for patients with dysphagia and is often sold at a fraction of the cost of commercially available capsules.[26]
  - » Antidepressants can be tried to reduce the frequency of episodes.[24]
- Seizure
  - » Seizures presenting within 1 week of stroke (early-onset seizures) are likely related to reversible injury and regarded as an acute symptom of the stroke.[27]
    - ° Although uncommon, status epilepticus can occur (see **Seizures - Status Epilepticus** monograph for insights / dosing for acute seizure management).[28]
    - ° The risk for recurrent seizure is low during this period; secondary prophylaxis is generally not recommended.
    - ° If anticonvulsants are started during this period, they should be withdrawn once the patients is out of the acute phase (7 days post-stroke); most patients will not experience future seizures.
  - » Seizures presenting ≥7 days after stroke (late-onset seizures) are unprovoked by the stroke itself, but rather are the result of more permanent changes to the brain.[27]
    - ° Because late-onset seizures carry a high risk of recurrence (>60%), they meet diagnostic criteria for epilepsy after a single seizure.[27]
    - ° Routine seizure prophylaxis is not recommended, but should be started if post-stroke epilepsy develops.[24,27-29]
    - ° Most seizures can be controlled with a single anticonvulsant.[28]
    - ° Available evidence does not support the use of a specific anticonvulsant; therapy should be selected with consideration for drug-interactions, adverse effects, route of administration, need for monitoring, and cost (see **Seizures - Prevention & Control** monograph).[19,28]
- Spasticity
  - » In many cases, patients with spasticity experience pain.[8]
  - » A distinction should be made between muscle spasm and spasticity, often occurring in the setting of neurological disease or injury.
    - ° Antispastic medications (eg, baclofen, tizanidine, diazepam) should be used for spasticity; other muscle relaxants are less likely to be effective. (See **Muscle Spasm / Spasticity** monograph).
  - » In cases of prolonged spasticity, muscle or joints can permanently shorten resulting in contractures which are associated with muscle rigidity and deformity.[8] Many patients with hemiparesis develop joint contractures on the affected side within a year of stroke.[19]
  - » Botulinum toxin injections are commonly used to treat spasticity in the upper and lower limbs of stroke patients.[18,19]
- Urinary incontinence
  - » See **Urinary Symptoms** monograph
  - » Problems range from urinary retention to complete incontinence including involuntary loss of urine, urge incontinence, and stress incontinence.[29]
  - » Urinary symptoms are more severe in stroke survivors compared to other patients with urinary incontinence and are associated with various downstream consequences that negatively impact quality of life (eg, depression, embarrassment, caregiver burden, contact dermatitis, skin breakdown, and pressure ulcers). [29]
  - » Behavioral interventions including bladder training for urge incontinence, pelvic floor muscle training for stress incontinence, and timed voiding may reduce incontinent episodes, but minimally impact quality of life.[29]

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIPLATELETS FOR PREVENTION[5,20]				
Aspirin (ASA)[10] (Bayer, St. Joseph Adult Aspirin)	Initial (primary prevention): 81mg PO QD Initial (secondary prevention): 81-325mg PO QD MDD: same as initial dosing	Capsule: 81mg, 325mg Capsule (ER)*: 162.5mg Chewable tablet: 81mg Tablet: 81mg, 325mg Tablet (buffered): 324mg, 325mg Tablet (DR)*: 81mg, 325mg Tablet (EC)*: 81mg, 325mg	**Antiplatelets** • Non-palliative • Use cautiously in patients with increased risk for bleeding / falls or who take other medications associated with bleeding (eg, NSAIDs, anticoagulants, antiplatelets) **ASA, ASA/Dipyridamole, Clopidogrel** • Upper GI events (incl. symptomatic ulcers) increased 2-4x, even at low doses; avoid in active peptic ulcer disease and consider adding gastroprotection (eg, PPI, H2RA) if combined with NSAIDs **ASA & ASA/Dipyridamole** • Avoid in severe liver impairment **Aspirin** • Not recommended for primary prevention in patients ≥70 years old due to increased risk for major bleeding, uncertain benefit **ASA/Dipyridamole** • Avoid if GFR <10 • Headache is common (39%); consider substitution or deprescribing • GI side effects are common (eg, abdominal pain, dyspepsia, n/v, diarrhea); avoid if history of active peptic ulcer disease • Dipyridamole causes peripheral vasodilation and may exacerbate hypotension or chest pain in CAD **Clopidogrel** • Contraindicated if active bleeding • Pro-drug, requires conversion to active metabolite by CYP2C19 enzyme; alternate therapy may be warranted in patients taking CYP2C19 inhibitors / inducers • Grapefruit juice may reduce serum levels, efficacy	Y/N*
ASA/Dipyridamole (Aggrenox)	Initial (secondary prevention): 25mg/200mg PO BID MDD: same as initial dosing	Capsule (ER): 25mg/200mg		N
Clopidogrel (Plavix)	Initial (secondary prevention): 75mg PO QD MDD: same as initial dosing	Tablet: 75mg, 300mg		Y

References

1. Zipes DP, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 11th ed. Philadelphia, PA: Elsevier; 2019.
2. Caplan LR, et al. Overview of the evaluation of stroke. UpToDate. (Lit review current through Jul 2021, accessed August 2021).
3. Furie KL, et al. Definition, etiology, and clinical manifestations of transient ischemic attack. UpToDate. (Lit review current through Jul 2021, accessed August 2021).
4. Rordorf G, et al. Spontaneous intracerebral hemorrhage: Pathogenesis, clinical features, and diagnosis. UpToDate. (Lit review current through Jul 2021, accessed August 2021).
5. Kernan WN, et al. Primary care of adult patients after stroke: a scientific statement from the American Heart Association/American Stroke Association. Stroke. 2021;52:e558–e571.
6. Klit H, et al. Central post stroke pain: clinical characteristics, pathophysiology, and management. Lancet Neurol. 2009;8:857-868.
7. Abdi S. Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis. UpToDate (Lit review current through July 2021, accessed August 2021).
8. Harrison RA, et al. Post stroke pain: Identification, assessment, and therapy. Cerebrovascular Diseases. 2015;39:190-201.
9. Gould RG, et al. Shoulder pain in hemiplegia. Medscape. Accessed online at: https://emedicine.medscape.com/article/328793-overview (Last updated Feb 2019)
10. Arnett DK, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140:e596–e646.
11. Samsa GP, et al. Epidemiology of recurrent cerebral infarction: Medicare claims-based comparison of first and recurrent strokes on 2-year survival and cost. Stroke.1999;30:338-349.
12. American Geriatrics Society 2019 Beers Criteria Update Expert Panel. American Geriatrics Society 2019 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674-694.
13. Kleindorfer DO, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke. 2021;52:e364-e467.
14. Progress Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358:1033-1041.
15. Sibon I, et al. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. Neurology. 2004;62:1187-1189.
16. Kutner JS, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA Intern Med. 2015;175(5):691-700.
17. Singh JA, et al. Botulinumtoxin for shoulder pain (Review). Cochrane Database of Systematic Reviews. 2010, Issue 9. Art. No.: CD008271.
18. Wissel J, et al. OnabotulinumtoxinA improves pain in patients with post-stroke spasticity: Findings from a randomized, double-blind, placebo-controlled trial. Journal of Pain and Symptom Management. 2016;52(1):17-26.
19. Winstein CJ, et al. Guidelines for adult stroke rehabilitation and recovery a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47:e98–e169.

Venous Thromboembolism

DEFINITIONS

A venous thromboembolism (VTE) is a venous blood clot (thrombus). VTE most commonly occur in deep veins **(deep vein thrombosis, DVT)** of the lower legs, thigh, or pelvis and less commonly in upper extremities. If a thrombus breaks loose, it can move (embolize) to the lungs **(pulmonary embolism, PE)**.

Thromboprophylaxis (TPX) refers to the use of anticoagulation to prevent VTE; it can be primary (patient at risk, but never had VTE) or secondary (prior history of VTE).

SYMPTOMS

- Many VTE occur in the hospice population without symptoms (subclinical VTE).[1-2]
  - » Approximately 10% of hospice patients will have symptomatic VTE and more than half will have subclinical VTE.[3]
- DVT symptoms can include unilateral pain, swelling, redness, and warmth of the affected area.
  - » Up to half of patients with DVT develop post-thrombotic syndrome (PTS), a chronic consequence of DVT that limits activity, reduces quality of life, and can cause symptoms like leg pain, intractable edema, lower leg skin thickening / discoloration / ulcers, itching, redness, and paresthesia. Similar symptoms in the upper extremities can follow upper extremity VTE.[4]
- PE symptoms can include chest pain, cough, dyspnea, hemoptysis, tachycardia, fatigue, cyanosis, and hypoxia.
- Besides physical symptoms, VTE can also cause acute and long-term psychological distress.[2,5-7]

CLINICAL INSIGHTS

- Hospice patients inherently have many risk factors for VTE (**Table 1**), so TPX should usually be considered related to the hospice plan of care.
  - » Cancer treatments and cancer itself are VTE risk factors, though the level of risk varies by the type / origin of cancer, with the highest risk seen in patients with cancers of the uterus, ovaries, brain, pancreas, stomach, kidney, and blood (lymphoma, leukemia).[13-14]
- Formal VTE diagnostic techniques (eg, ultrasound for DVT; D-dimer testing / VQ scan / CTPA for PE) are almost never employed in the hospice setting. DVT is often diagnosed presumptively based on recognizable symptoms, but PE, which cause relatively indiscriminate symptoms, are less commonly diagnosed and symptoms are often attributed to other pathologies.[1,7,15]
- TPX for primary prophylaxis is nearly always inappropriate for hospice patients, but it is often considered for secondary prophylaxis if benefits are deemed to outweigh risks.[2,6,15]
- VTE treatment guidelines, predictive risk models (eg, Khorana score), and bleeding risk models (eg, HAS-BLED, VTE-BLEED) rely on data that exclude hospice patients due to their short prognosis and significant morbidity; therefore, their applicability to the hospice population is questionable.[5]
- VTE are often symptomatic, but it is currently unknown if TPX improves symptom burden or quality of life for hospice patients. Likewise, it is not known if TPX extends the prognosis of hospice patients or whether deprescribing hastens death.[1,2,5-6]
- Some clinicians perceive sudden PE as a rapid and preferable cause of death, despite evidence that the majority of deaths attributed to PE are neither sudden nor asymptomatic.[2,16]
  - » Those experiencing fatal PE take an average of 2 hours to die, and the event is typically preceded by significant breathless, tachycardia, and fever.[7]
- The vast majority of VTE symptoms, including pain, angina, dyspnea, and cough can be palliated with opioids and other traditional end-of-life medications.[6,15]
- PTS symptoms typically improve with rest and leg elevation and worsen when upright.[4]
  - » There is no evidence that diuretics improve edema associated with PTS.[4]
  - » Ulcers associated with PTS are notoriously slow to heal and can occur with minor trauma.[4]
- Consider patient prognosis and likelihood of subsequent VTE when weighing the potential palliative benefit of TPX (**Figure 1**).

- » Patients may derive a psychological palliative benefit and improved quality of life from TPX, reporting that it gives them feelings of safety / reassurance and that active interventions are occurring despite the hopelessness of their clinical situation.[2]

- Several anticoagulants can be used for TPX, each with their own pros and cons (**Table 2**)
- Unless a patient prefers to wear them, compression stockings are inappropriate in the hospice setting because they typically decrease quality of life, commonly causing itching, sweating, and discomfort.[2]
- Considering the uncertainty surrounding the benefits TPX in the hospice setting, as well as the high costs associated with anticoagulation, hospice agencies should consider developing their own formal policies that reflect their viewpoints.[2,15]

DEPRESCRIBING

- When TPX is prescribed to hospice patients, its appropriateness should be reviewed daily.[2]
- Deprescribing discussions should be individualized and consider patient and provider preference in addition to the estimated benefits vs. risks of TPX.[2]
  - » Some patients at high risk for bleeding may prefer to remain anticoagulated instead of deprescribing TPX due to fear of VTE.[15]
- Factors that should prompt consideration for deprescribing TPX include:
  - » Active bleeding / high bleeding risk – risk factors include advanced age, malignancy, heart disease, liver disease, renal disease, diabetes, bleeding history, anemia, concomitant use of drugs that also increase bleeding risk (eg, NSAIDs, antiplatelets), poor performance status.[5,14,17]
    - ° Antithrombotic-induced bleeding is a common cause of emergency department admissions.[18]
    - ° Nearly 10% of patients with cancer experience clinically relevant bleeding at the end of life and about 1 in 5 of these events contributes to death.[19]
  - » Recent fall / high fall risk – hospice patients are inherently at risk for falls, which increase the risk of subsequent bleeds, including intracranial hemorrhage.[17]
  - » Dysphagia / decreased caloric intake – particularly if warfarin being used for TPX.[17]
  - » Decline in performance status / prognosis[2]
  - » Changing goals of care[5]
  - » Patient / family preference[5]
- When a decision to deprescribe is made, TPX can be abruptly deprescribed without taper.
- Replacing TPX with daily aspirin (so called "de-escalation"), with the perceived benefits of reduced bleeding risk and better alignment with goals of care, is relatively common in the hospice setting, but is not an evidence-based practice.[20] It is often considered if TPX is deemed futile, but patient / family wish for an active intervention of any sort.[15]

TABLE 1: PALLIATIVE HEART FAILURE MEDICATIONS [2,5,8-12]

Risk Factor	Comments
Prior VTE	• Strongest known risk factor (esp. PE, proximal DVT) • Risk is highest in first 180 days after VTE
Age	• Risk increases with each year of life • VTE incidence in those ≥75 years old is 7-10x greater than in adults ≤55 years old
Hypercoagulable states	• Malignancy • Metastatic burden (esp. liver, bone metastases) • Inflammatory bowel disease
Blood stasis	• Major medical illness (esp. Cancer, CHF, ESLD, ESRD) • Immobility / paralysis • Sepsis • Lower limb edema
Vascular injury	• Trauma (esp. hip / leg / pelvis fracture) • Central venous catheter
Drugs	• Megestrol • Glucocorticoids • Erythropoietin • Tamoxifen • Recent IV drug abuse

FIGURE 1: CONCEPTUALIZING POSSIBLE PALLIATIVE BENEFIT WITH TPX IN HOSPICE PATIENTS[15]

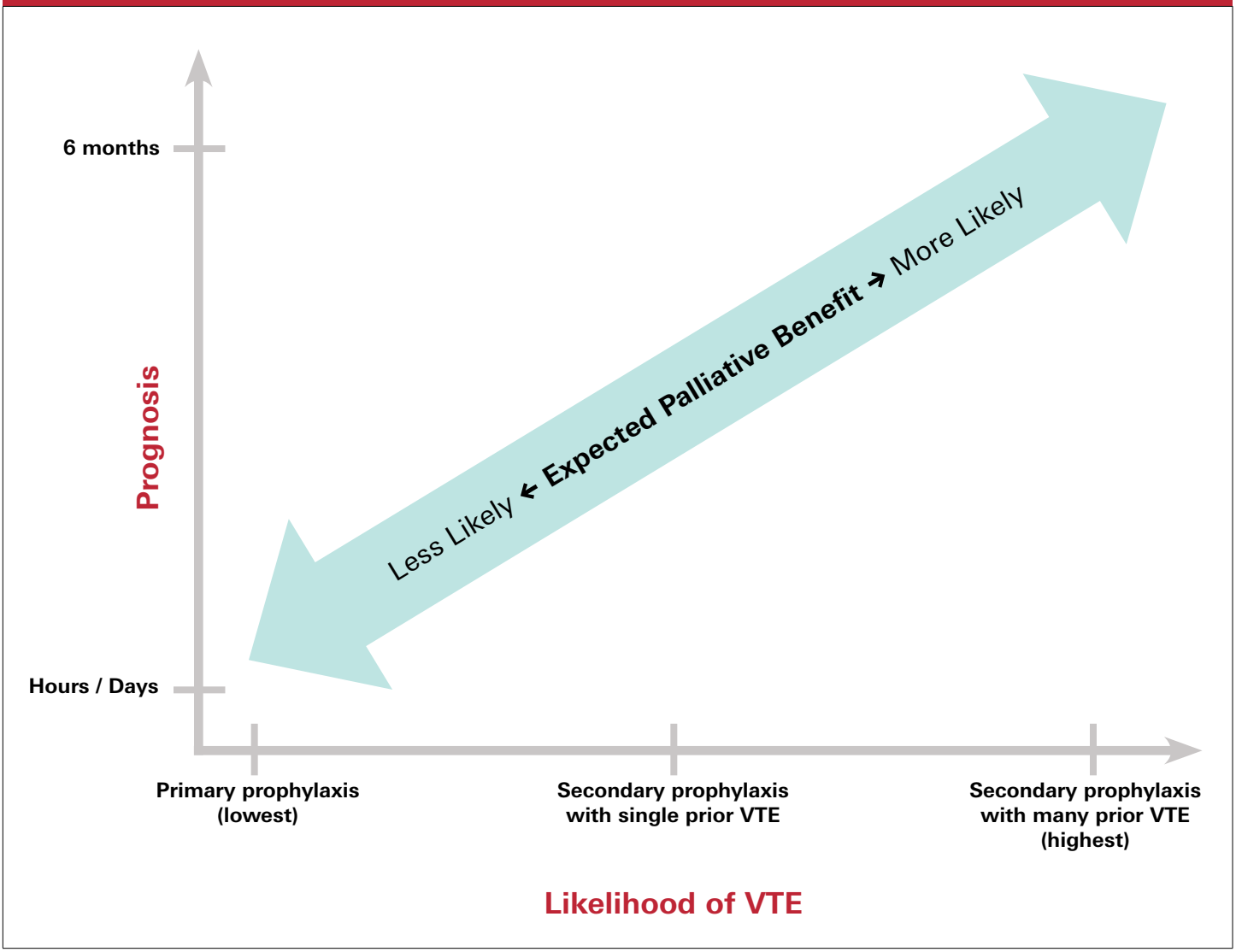


TABLE 2: PROS AND CONS OF ANTICOAGULANTS USED FOR TPX

Anticoagulant	Pros	Cons
Warfarin	• Inexpensive • Convenience of oral route and once daily dosing • Preferred oral agent if severe renal impairment	• Narrow therapeutic index drug that requires INR monitoring that can decrease quality of life and treatment compliance. • INRs are more labile in hospice patients and even with more frequent lab monitoring, INRs are frequently outside of therapeutic range • Higher risk of bleeding in cancer and hospice settings[6] • Numerous drug interactions are problematic as drugs are frequently added and deprescribed in the hospice setting • Dietary vitamin K affects anticoagulant effect and inconsistent diet is common for hospice patients • Reversal agent (vitamin K) is expensive • Best avoided in severe liver disease, since INR is inherently elevated and may not reflect the effect of warfarin[12]
Novel oral anticoagulants (NOACs)	• No lab monitoring required • Convenience of oral route and once or twice daily dosing • Less interactions with food and drugs than warfarin • Drugs of choice for most VTE, unless cancer or severe renal impairment[12]	• Expensive • Reversal agents are expensive and require hospitalization to administer • Require renal dose adjustment if mild-moderate renal impairment; contraindicated with severe impairment
Low-molecular weight heparin (Typically enoxaparin)	• Drug of choice for cancer-related VTE • Convenient once daily dosing • Minimal drug interactions • Routine lab monitoring not required • Heparin-induced thrombocytopenia (HIT) less common than with heparin	• Expensive • Requires patient or caregiver to administer injections, although they are generally well tolerated • Require renal dose adjustment if mild-moderate renal impairment; contraindicated with severe impairment
Heparin	• Inexpensive • Preferred over enoxaparin in those with significant renal impairment	• HIT may occur • Hospice clinician unfamiliarity • Activated partial thromboplastin time (APTT) is monitored in most settings, though unmonitored outpatient regimens have been published. • Requires patient or caregiver to administer injections, although they are generally well tolerated • Reversal agent (protamine sulfate) exists, but would require hospitalization to administer

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NOVEL ORAL ANTICOAGULANTS[21]				
Apixaban (Eliquis)	Initial: 10mg PO BID x 7 days then 5mg BID For some high risk patients, continued TPX beyond 6 months may be warranted. In these cases, reduced intensity dosing (2.5mg BID) can be considered. MDD: same as initial dosing	Tablet: 2.5mg, 5mg	• Preferred NOAC if CrCl <15ml/min • Avoid if severe hepatic impairment • Significant drug interactions with CYP3A4 inhibitors / inducers • If 2.5mg dose indicated, consider using ½ of 5mg tablet to reduce spend	Y
Dabigatran (Pradaxa)	Initial: Following ≥5 days of heparin/ LMWH, 150mg PO BID MDD: same as initial dosing	Capsule: 75mg, 110mg, 150mg	• Avoid if CrCl <30ml/min • Preferred NOAC if severe hepatic impairment • Not recommended in patients ≥75 years old due to increased risk for GI bleeding • *Swallow capsules whole; removing capsule shell leads to significant increase in absorption and risk for serious adverse effects, including fatal bleeding • Must be stored in manufacturer's container / package to protect from moisture; capsules dispensed in bottle should be used within 4 months of opening	N*
Edoxaban (Savaysa)	Initial: Following ≥5 days of heparin/ LMWH, 60mg PO QD Reduced dose (30mg PO QD) recommended if any one of the following: • weight ≤60 kg • CrCl 15-50ml/min • Taking potent P-glycoprotein inhibitor MDD: same as initial dosing	Tablet: 15mg, 30mg, 60mg	• Efficacy may be reduced if CrCl >95ml/min • Adjust dose if CrCl between 15-50ml/ min; avoid if <15ml/min. • Avoid if moderate-severe hepatic impairment	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NOVEL ORAL ANTICOAGULANTS[21] (CONTINUED)				
Rivaroxaban (Xarelto)	Initial: 15mg PO BID x 21 days, then 20mg QD For some high risk patients, continued TPX beyond 6 months may be warranted. In these cases, reduced intensity dosing (10mg QD) can be considered. MDD: same as initial dosing	Tablet: 2.5mg, 10mg, 15mg, 20mg	• Significant drug interactions with CYP3A4 inhibitors / inducers • Not recommended in patients ≥75 years old due to increased risk for GI bleeding • Avoid if CrCl <30ml/min • Avoid if moderate-severe hepatic impairment • Administer doses ≥15mg with food to ensure adequate bioavailability • Avoid concomitant use with drugs that are strong CYP3A4 / P-glycoprotein inhibitors (eg, ketoconazole) or inducers (eg, carbamazepine, phenytoin, rifampin) • If 10mg dose indicated, consider using ½ of 10mg tablet to reduce spend	Y
HEPARINS[21]				
Heparin (unfractionated; UFH)	Initial: 333 units/kg SQ x 1 dose, then 250 units/kg every 12 hours MDD: same as initial dosing	Solution for injection: Pre-filled syringe: 5,000 units/0.5ml Vials 1 unit/ml; 10 units/ml; 100 units/ml; 1,000 units/ml; 5,000 units/0.5ml; 5,000 units/ml; 10,000 units/ml; 20,000 units/ml	• Used to bridge to NOAC (dabigatran or edoxaban) or warfarin • Generally reserved for patients who have contraindication to other anticoagulants • Alternate injection sites • IV infusions unlikely to be used in hospice setting • Serum levels may be increased in patients >60 years old; lower doses may be necessary[22]	-
Enoxaparin (Lovenox)	Initial: 1mg/kg SQ every 12 hours or 1.5mg/kg SQ QD MDD: same as initial dosing	Solution for injection: 30mg/0.3ml, 40mg/0.4ml, 60mg/0.6ml, 80mg/0.8ml, 100mg/ml, 120mg/0.8ml, 150mg/1ml	• Low molecular weight heparin • Used to bridge to NOAC (dabigatran or edoxaban) or warfarin or as monotherapy • Preferred anticoagulant for patients with cancer • Doses commonly rounded to nearest 10mg • Requires renal dose adjustments • Injection-associated bleeding/bruising more common in elderly patients, esp. if weight <45kg	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
WARFARIN				
Warfarin (Coumadin, Jantoven)	Initial: (Note: requires ≥5 days of concomitant heparin/LMWH until therapeutic INR confirmed.) Individualized dosing protocols exist. The most common starting dose is 5mg QD with 2.5mg QD preferred for those expected to be sensitive to warfarin (eg, frail, elderly, malnourished, renal / hepatic disease, CHF, concomitant use of drug(s) that increase warfarin levels) Pharmacogenomic-guided dosing algorithms have been published and can be used when genotype results are available MDD: individualized based on INR levels.	Tablet: 1mg, 2mg, 2.5mg, 3mg, 4mg, 5mg, 6mg, 7.5mg, 10mg	• For eligible patients, DOACs have supplanted warfarin as the medical standard of care • In the hospice setting, drug regimens change regularly and dietary intake is often inconsistent making warfarin use problematic due to many drug and food interactions • PT/INR monitoring required (at least monthly, if stable INR); target INR = 2 to 3 for VTE treatment[23] • Even with more frequent therapeutic monitoring, hospice patients are often out of range.[24] • Caution in renal / hepatic impairment	Y

References

1. Sandset, PM et al. Is venous thromboembolism a problem with cancer in palliative care?, *The Lancet*, 2019; 6: 1-2.
2. Zabrocka, E et al. Thromboprophylaxis in cancer patients in hospice, *Adv Clin Exp Med*, 2018; 27(2): 283-9.
3. Johnson, MJ et al. Primary thromboprophylaxis in hospices: The association between risk of vein thromboembolism and development of symptoms, JPSM, 2014; 48: 56-64.
4. Kahn, S. The post-thrombotic syndrome, *Hematology*, 2016; 1: 413-18.
5. Zabrocka, E et al. Thromboprophylaxis in the end-of-life cancer care – the update, *Cancers*, 2020; 12, 600.
6. Chin-Yee, N et al. Thromboembolic disease in palliative and end-of-life care: A narrative review, *Thrombosis Research*, 2019; 175 84-9.
7. Noble, S. Thromboembolic disease and breathlessness, *Curr Opin Supprt Palliat Care*, 2016; 10: 249-55.
8. Dipiro et al. Pharmacotherapy: a pathophysiology approach. 11th Ed. Chapter 37. Venous thromboembolism.
9. Anderson FA et al. Risk factors for venous thromboembolism. Circulation. Jun 2003. https://www.ahajournals.org/doi/pdf/10.1161/01.cir.0000078469.07362.e6
10. Cushman MC. Epidemiology and risk factors for venous thrombosis. NIH. April 2007. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2020806/pdf/nihms21418.pdf
11. Bauer, K et al. Overview of the cause of venous thrombosis, *UpToDate*, information current through August 2021.
12. Hull, R et al. Venous thromboembolism: anticoagulation after initial management, *UpToDate,* information current through Aug 2021.
13. NICE guidelines – Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital, appendix D – evidence tables, p. 92.
14. Cai, R et al. Thromboprophylaxis for inpatients with advanced cancer in palliative care settings: A systematic review and narrative synthesis, *Palliative Medicine*, 2019; 33(5): 486-99.
15. Author opinion / experience.
16. Gurau, A et al. Primary Thromboprophylaxis in Individuals without Cancer Admitted to A Geriatric Palliative Care Unit, JAGS, 2018; 66: 346-9.
17. National Hospice and Palliative Care Organization (NHPCO) Hospice Medication Deprescribing Toolkit, Nov. 2020, v.1.0, accessed online Sept. 2021 at: file:///C:/Users/jsolien/Downloads/NHPCO_Deprescribing_Toolkit%20(1).pdf
18. Budnitz, DS et al, Emergency hospitalizations for adverse drug events in older Americans, *NEJM*, 2011; 365: 2002-12.
19. Huisman, B et al. Use of antithrombotics at the end of life: an in-depth chart review study, *BMC Palliative Care*, 2021; 20: 110.
20. Kowalewska, C et al. Prevalence and clinical intentions of antithrombotic therapy on discharge to hospice care, *J Pall Med*, 2017; 20(11): 1225-30.
21. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.
22. Hull RD, et al. Heparin and LMW heparin: Dosing and adverse effects. UpToDate (Lit review current through Aug 2021, accessed Sept 2021).
23. Kearon C et al. Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;142(6):1698-1704.
24. Hill RR, et al. A descriptive evaluation of warfarin use in patients receiving hospice or palliative care services. J Thromb Thrombolysis. 2009;27:334–339.

Diabetes

DEFINITION

Diabetes mellitus is a disease of abnormal carbohydrate metabolism characterized by hyperglycemia resulting from insufficient insulin secretion by pancreatic beta-cells (β-cells).

Type 1 diabetes (DM1) is the result of autoimmune or idiopathic destruction of β-cells leading to absolute insulin deficiency.

Type 2 diabetes (DM2) is the result of a progressive loss of β-cell insulin secretion characterized by hyperglycemia with varying degrees of insulin deficiency and resistance. DM2 is more common than DM1.

Brittle diabetes, or labile diabetes, describes severe instability of blood glucose levels that are unpredictable and disruptive to daily life.

Hypoglycemia blood glucose <70mg/dL

Symptomatic hyperglycemia usually occurs with blood glucose exceeding 300mg/dL, leading to hallmark symptoms of hyperglycemia (increased thirst, increased urination, and blurred vision).

CAUSES [1, 2]

- Genetic and environmental factors can lead to the progressive loss of pancreatic β-cell mass or function.
- Diseases that damage the pancreas or involve removal of pancreatic tissue (diseases of the exocrine pancreas)
  - » Cancer
  - » Pancreatitis
  - » Hereditary hemochromatosis
  - » Cystic fibrosis
- Endocrine disorders
  - » Cushing's syndrome
  - » Acromegaly
  - » Pheochromocytoma
  - » Glucagon-secreting tumors (glucagonoma)
  - » Somatostatin-secreting tumors (somatostatinomas)
  - » Hyperthyroidism (due to interference with glucose metabolism)
- Medications
  - » Corticosteroids (most common with systemic glucocorticoids)
  - » Select antipsychotics (more common with olanzapine, chlorpromazine, clozapine)
  - » Thiazide diuretics
  - » HIV antiretrovirals (protease inhibitors and nucleoside transcriptase inhibitors)
  - » Most beta-blockers (more common with atenolol, metoprolol, and propranolol; carvedilol doesn't appear to impair glucose tolerance)
  - » Select cholesterol-lowering drugs (niacin, statins)
  - » Gonadotropin-releasing hormone agonists (class effect in men receiving androgen deprivation therapy for metastatic prostate cancer)
  - » Hormones (megestrol, progestins, growth hormones)
  - » Immunosuppressants (cyclosporine, tacrolimus, sirolimus)
  - » Moxifloxacin (rare)
- Obesity

HOW TO RECOGNIZE SYMPTOMS

- Hyperglycemia
  - » Symptoms include increased urination, thirst, and blurred vision (**Table 1**).[3]
  - » Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are states of extreme hyperglycemia and cause additional symptoms (**Table 1**). Left untreated, they can cause severe neurologic symptoms and may progress to coma/death.[4]
- Hypoglycemia
  - » Not a symptom of diabetes, but rather a consequence of overtreatment of diabetes that results in various symptoms, some of which overlap with those seen in hyperglycemia (**Table 1**)
    - ° Hypoglycemia unawareness occurs when a patient does not experience or notice hypoglycemia symptoms and can delay diagnosis and treatment. Risk factors include frequent hypoglycemic episodes, longstanding diabetes, and tight blood glucose control.
  - » Because of diminishing oral intake and inconsistent diet, hospice patients receiving

treatment with antidiabetic medications/insulin are at higher risk for developing hypoglycemia (**Table 2**).

- » Existing orders for glucagon or glucose replacement gel/tabs typically indicate history of a hypoglycemic event.
- » Hypoglycemia risk is highest with insulin and sulfonylureas, so their presence in drug regimens should prompt consideration of hypoglycemia when characteristic symptoms occur.
- » If unexplained hypoglycemia occurs in a patient receiving a synthetic opioid like tramadol or methadone, drug-induced hypoglycemia should be considered in the differential diagnosis.[5–7]

TABLE 1 – SYMPTOMS OF HYPERGLYCEMIA AND HYPOGLYCEMIA[3]

HYPERGLYCEMIA		HYPOGLYCEMIA
• Increased thirst • Increased urination • Blurred vision* • Increased hunger* • Dehydration • Confusion*		• Feeling shaky, lightheaded, or dizzy • Anxiety, nervousness • Weakness, drowsiness • Sweating, chills, feeling "clammy" • Irritability • Confusion* • Tachycardia • Increased hunger* • Nausea • Blurred vision* • Headaches • Seizure*
Diabetic Ketoacidosis (DKA) • BG 250-800mg/dL • More common in DM1 • Hyperventilation • Abdominal pain • Sweet and fruity odor on breath	**Hyperosmolar Hyperglycemic State (HHS)** • BG > 600mg/dL • More common in DM2 • Neurologic symptoms (eg, obtundation, seizure*, coma)	

* Can occur with both hyper/hypoglycemia

TABLE 2 – RISK FACTORS FOR HYPOGLYCEMIA

- Longer duration of diabetes
- Treatment with insulin, sulfonylureas, or meglitinides and/or:
  - » inadequate carbohydrate consumption following their administration*
  - » alcohol consumption
  - » physical activity and unchanged medication dose/carbohydrate consumption
- Sudden reduction of corticosteroid doses*
- Polypharmacy (≥5 medications; esp. ACE inhibitors, angiotensin receptor blockers, nonselective β-blockers)*
- History of hypoglycemia
- Inability to go grocery shopping or prepare meals*
- Renal/hepatic impairment*
- Cognitive impairment*
- Malabsorption/dysphagia*

* Denotes more common in hospice patients

CLINICAL INSIGHTS

- Diabetes management at end-of-life should be symptom-driven (ie, prevent symptomatic hyperglycemia and hypoglycemia) and should not be based solely on blood glucose measurements.
  - » Microvascular (eg, retinopathy, nephropathy, neuropathy) and macrovascular (eg, CAD, cerebrovascular disease, PAD) complications of diabetes develop over time periods that exceed the 6-month prognosis of hospice patients. Therefore, traditional / guideline-based treatment approaches focused on preventing these complications should not be applied to hospice patients.
- Liberalized blood glucose targets of 200 to 300mg/dL (or similar) have been recommended to reduce hypoglycemia risk in hospice patients. Most will not experience hyperglycemic symptoms in this range.[1,8]
  - » With liberal targets, quality of life may improve by reducing pill burden, drug side effects, monitoring, fingersticks, and injections.
  - » Liberal targets often facilitate deprescribing of short/rapid-acting insulins in DM1 and insulin and oral antidiabetic drugs in DM2.
  - » Patient selection for application of liberal blood glucose targets:

- Most diabetic hospice patients will benefit, especially those with prior or recent hypoglycemic episodes
- Targets should be applied more cautiously in patients with a history of DKA or HHS

- Insulin selection and dosing
  - Most hospice patients wish to die at home, but patients ≥80 years old treated with insulin are more than 2-times as likely to visit emergency departments and 5-times more likely to be hospitalized for insulin-related hypoglycemia/errors.[9]
  - Insulin dosing is highly individualized and regimens are usually in place prior to patients electing the hospice benefit. It is rare to initiate insulin therapy in hospice patients.
    - Typical dosing in DM1 (non-hospice population)[10]
      - Initial: 0.2 to 0.5 units/kg/day with 40-50% of that amount given as basal insulin (divided once or twice daily) and 50-60% given as divided bolus insulin doses with meals.
      - Usual: 0.4 to 1 unit/kg/day as above.
    - Initial dosing in DM2 depends on the type of insulin selected and patient weight can be considered.
    - Dosing and administration insights for hospice patients
      - Sliding-scale insulin regimens should be avoided.[11, 12]
      - For basal dosing, "peakless" long-acting insulins (glargine and degludec) are likely preferred in the hospice setting (**Table 3**) because they are less likely to cause hypoglycemia.
      - Depending on patients' ability to eat and the extent to which their meals cause hyperglycemia, they may or may not require mealtime insulin.
        - If mealtime insulin is warranted, rapid-acting insulins are likely preferred to minimize lag between administration and meal consumption to prevent hypoglycemia in case the meal is not consumed as expected.
  - While regular insulin is the least expensive insulin currently available, diabetic patients have died following cost-driven switches from insulin analogs.[13]
    - Therapeutic substitution with regular insulin in place of analogs to reduce costs should not be attempted in DM1 patients and only cautiously in DM2 patients.[13, 14]

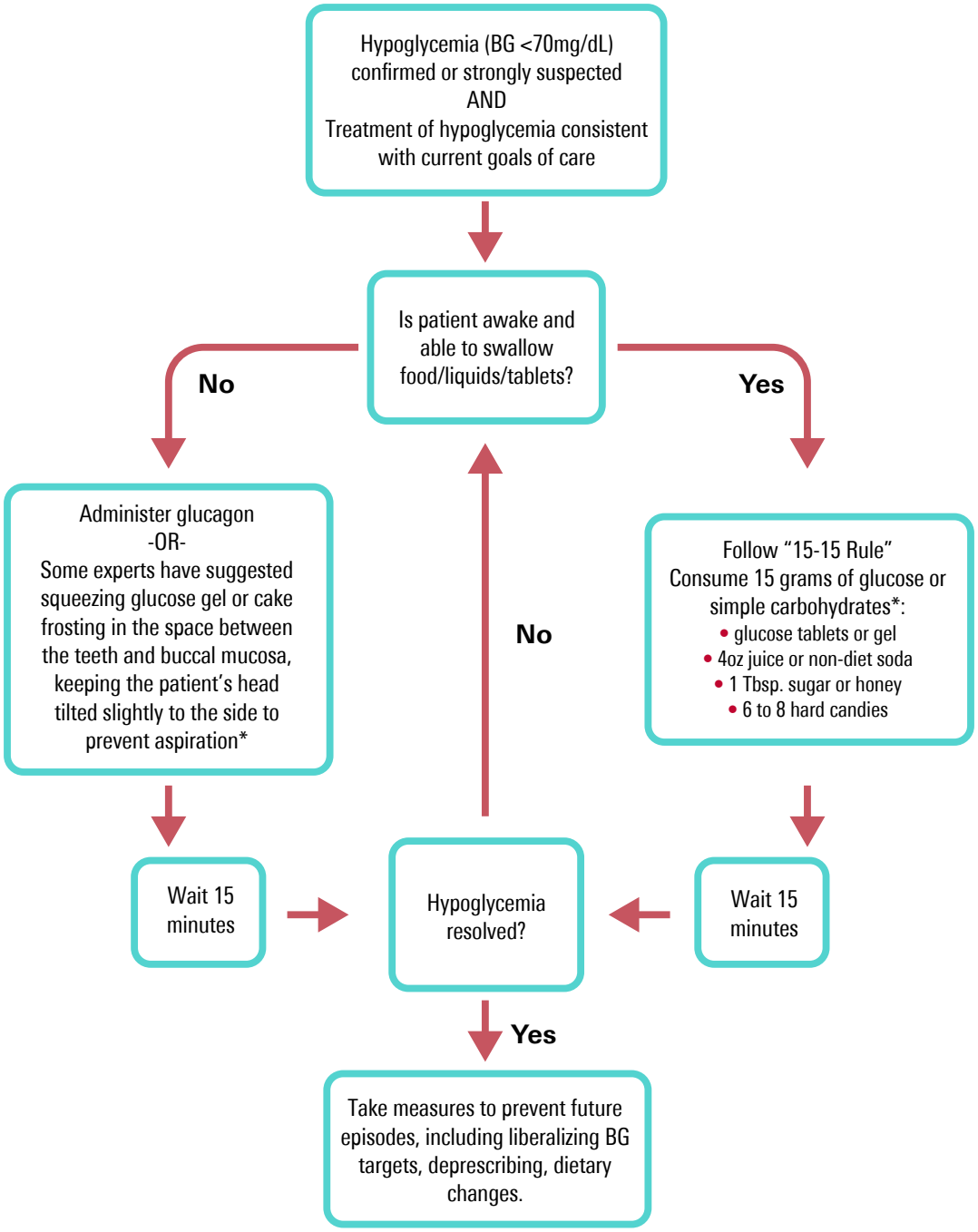
- Hypoglycemia can still occur despite liberalized blood glucose targets and other efforts to prevent it.
  - If correcting the hypoglycemia is consistent with established goals of care, see OPPC Hypoglycemia Treatment Algorithm (**Figure 1**)
  - If hypoglycemia leads to unconsciousness in an actively dying patient, it is reasonable to provide supportive care only by addressing the symptoms of hypoglycemia without correcting the hypoglycemia.[17]

- Drug adverse effects and interactions
  - Corticosteroids can cause dose-dependent hyperglycemia in patients with and without preexisting diabetes.[18] This is usually observed with systemic steroids, but may transiently occur following intra-articular administration.[19]
    - Onset is highly variable and resolution of hyperglycemia may take several days to weeks following steroid discontinuation.[20]
    - Anticipate the need to add or modify diabetes medications when starting or stopping systemic steroids.
  - Pioglitazone and rosiglitazone can cause fluid retention and worsen heart failure.[10, 12]
  - Metformin is contraindicated in patients with advanced renal impairment due to increased risk for lactic acidosis, a rare but potentially fatal condition that may be accompanied by symptoms including myalgias, respiratory distress, and abdominal pain.[10]

- Hospice medication coverage
  - Although not commonly a stand-alone terminal diagnosis, diabetes can contribute to a patient's terminal prognosis. In these cases, we recommend hospice coverage of antidiabetic drugs and supplies.

- We also recommend hospice coverage for patients with terminal pancreatic cancer.
- CMS recommends coverage of antidiabetics for steroid-dependent patients due to the potential for steroid-induced hyperglycemia.[21]
  - Other drugs known to cause hyperglycemia include antipsychotics, beta-blockers, anti-retrovirals, and thiazide diuretics.

FIGURE 1 – OPPC HYPOGLYCEMIA TREATMENT ALGORITHM FOR HOSPICE PATIENTS[15, 16]



*If patient takes insulin or insulin secretagogue (sulfonylureas or glinides) PLUS an alpha-glucosidase inhibitor, only dextrose/glucose should be used. Sucrose-containing products will be less effective in raising blood sugar.

TABLE 3 – INSULIN PRODUCTS AND KEY PROPERTIES [1, 10]

INSULIN TYPE	BRAND	ONSET	PEAK	DURATION	DOSING	TIMING	STABILITY AFTER FIRST USE (DAYS)
BASAL INSULIN **MAINTAINS NORMAL BLOOD GLUCOSE DURING PERIODS OF FASTING**							
Intermediate-Acting							
NPH	Humulin N	1 – 2 hours	4 – 12 hours	14 – 24 hours	BID – QID	-	31 (vial) 14 (pen)
	Novolin N	1 – 2 hours	4 – 12 hours	14 – 24 hours	BID – QID	-	42 (vial) 14 (pen)
Long-Acting							
Detemir	Levemir	3 – 4 hours	3 – 9 hours	6 – 23 hours	QD – BID	If QD dosing: PM or HS	42 (vial/pen)
Glargine	Lantus	3 – 4 hours	No peak	> 24 hours	QD – BID	Give at same time each day	28 (vial/pen)
	Basaglar	unavailable	No peak	> 24 hours	QD – BID	Give at same time each day	28
	Toujeo	6 hours	No peak	> 24 hours	QD – BID	Give at same time each day	56
NPL	Humalog 50/50	15-30 minutes	48 – 288 minutes	14 – 24 hours	BID – TID	Within 15 minutes before meal(s)	28
	Humalog 75/25	15-30 minutes	1 – 6.5 hours	14 – 24 hours	BID – TID	Within 15 minutes before meal(s)	28
Ultra-Long-Acting							
Degludec	Tresiba	1 hour	9 hours	> 40 hours	QD	-	56 (vial/pen)
BOLUS INSULIN (AKA PRANDIAL OR MEALTIME INSULIN) **COVERS INSULIN REQUIREMENTS AFTER FOOD ABSORPTION**							
Rapid-Acting							
Aspart	Novolog	12 – 18 minutes	1 – 3 hours	3 – 5 hours	QD – TID	Within 5 – 10 minutes before meal(s)	28 (vial/pen)
	Fiasp	7-13 minutes	90 – 132 minutes	5 – 7 hours	QD – TID	Within 20 minutes after starting meal(s)	28 (vial/pen)
Glulisine	Apidra	12 – 30 minutes	96 – 168 minutes	3 – 4 hours	QD – TID	Within 15 minutes before or within 20 minutes after starting meal(s)	28 (vial/pen)
Lispro	Admelog, Humalog	15-30 minutes	0.5 – 2.5 hours	< 5 hours	QD – TID	Within 15 minutes before or immediately after meal(s)	28 (vial/pen)
Short-Acting							
Regular (100 units/ml)	Humulin R	15-30 minutes	2.5 – 5 hours	4 – 12 hours	QD – TID	Within 30 minutes before meal(s)	31
	Novolin R	15-30 minutes	2.5 – 5 hours	4 – 12 hours	QD – TID	Within 30 minutes before meal(s)	42

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
BIGUANIDE [1, 10]				
Metformin (Fortamet, Glucophage, Glumetza, Riomet)	Initial (IR): 500mg PO QD-BID Initial (ER): 500mg PO QD MDD (IR): 2,550mg/day eGFR 30-45: 1,000mg/day MDD (ER): 2,000mg/day	Oral solution: 500mg/5ml Tablet (ER)*: 500mg, 750mg, 1,000mg Tablet (IR): 500mg, 850mg, 1,000mg	• Deprescribe when possible • Increases insulin sensitivity • GI adverse effects (eg, diarrhea, nausea, vomiting, flatulence) are common • Minimize GI effects by taking with food or giving IR doses >2,000mg/day in 3 divided doses • Risk of lactic acidosis, a rare but potentially fatal adverse effect, is increased with renal/hepatic impairment, dehydration, hypoxia and excess alcohol use. • Contraindicated in severe renal impairment (eGFR <30) • Oral solution is expensive	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
SULFONYLUREAS[1, 10]				
Glimepiride (Amaryl)	Initial: 1-2mg PO QD MDD: 8mg/day	Tablet: 1mg, 2mg, 4mg	**Sulfonylureas** • Deprescribe when possible • Increases insulin sensitivity from pancreatic β-cells • Give with meals at the same time each day; hold doses for reduced oral intake/skipped meals • Hypoglycemia is the most common adverse effect and risk is increased in patients with reduced caloric intake, CKD, and concomitant use of other antidiabetic agents. **Glipizide** • Preferred sulfonylurea in older patients due to shorter duration of action • Renal dose adjustments required **Glimepiride & Glyburide** • Long duration of action; not recommended in elderly patients due to risk for severe hypoglycemia **Glyburide** • Conventional and micronized tablet doses are not bioequivalent or interchangeable; 10mg conventional ≈ 6mg micronized • Not recommended for use in CKD due to risk for accumulation of active metabolites • Doses >10mg/day (conventional) or >6mg/day (micronized) may be given in divided doses BID for improved drug response	Y
Glipizide (Glucotrol)	Initial (IR): 2.5mg PO QD Initial (ER): 2.5-5mg PO QD MDD (IR): 40mg/day (doses >20mg/day not more effective) MDD (ER): 20mg/day	Tablet: 5mg, 10mg Tablet (ER)*: 2.5mg, 5mg, 10mg		Y/N*
Glyburide (Diaβeta, Glynase, Micronase)	Initial (conventional): 2.5-5mg PO QD Initial (micronized): 1.5-3mg PO QD MDD (conventional): 20mg/day MDD (micronized): 12mg/day	Tablet (conventional): 1.25mg, 1.5mg, 2.5mg, 3mg, 5mg, 6mg Tablet (micronized): 1.5mg, 3mg, 6mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MEGLITINIDES [1, 10]				
Nateglinide (Starlix)	Initial: 60-120mg PO TID, 30 minutes before meals MDD: 360mg/day	Tablet: 60mg, 120mg	**Meglitinides** • Deprescribe when possible • Increases insulin sensitivity from pancreatic β-cells; reduce mealtime glucose • If meal is skipped, hold scheduled dose to avoid hypoglycemia • Adverse effects include hypoglycemia, upper respiratory tract infection, back pain, flu-like symptoms, dizziness, arthropathy, and diarrhea • Require renal dosing adjustment	Y
Repaglinide (Prandin)	Initial: 0.5-2mg PO 30 minutes before each meal (BID-QID). CrCl 20-40ml/min: 0.5mg PO with meals. MDD: 16mg/day	Tablet: 0.5mg, 1mg, 2mg		Y
THIAZOLIDINEDIONES (TZDS) [1, 10]				
Pioglitazone (Actos)	Initial: 15-30mg PO QD MDD: 45mg/day	Tablet: 15mg, 30mg, 45mg	**TZDs** • Deprescribe when possible • Increases insulin sensitivity • Avoid if symptomatic heart failure, bladder cancer, fall/fracture risk, active liver disease • May cause dose-dependent edema and worsen heart failure symptoms. • Additional adverse effects include weight gain, headache, respiratory tract infections, bone fractures	Y
Rosiglitazone (Avandia)	Initial: 4mg PO QD (or in 2 divided doses) MDD: 8mg/day	Tablet: 2mg, 4mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DPP-4 INHIBITORS [1, 10]				
Alogliptin (Nesina)	Initial/MDD: 25mg PO QD	Tablet: 6.25mg, 12.5mg, 25mg	**DPP-4 inhibitors** • Deprescribe when possible • Increases insulin sensitivity • Discontinue in patients receiving GLP-1 agonists due to lack of incremental benefit • Adverse effects include headache, joint/muscle pain, respiratory tract infection, pancreatitis • Dose reductions may be needed if used with sulfonylureas or insulin due to increased hypoglycemia risk • Expensive **Sitagliptin, Saxagliptin, Alogliptin** • Renal dose adjustments required **Alogliptin & Saxagliptin** • May cause/worsen heart failure **Alogliptin** • May cause hepatoxicity **Saxagliptin** • May cause peripheral edema • Avoid use in heart failure • Limit dose to 2.5mg/day if taking strong CYP3A4/5 inhibitors	Y
Linagliptin (Tradjenta)	Initial/MDD: 5mg PO QD	Tablet: 5mg		Y
Saxagliptin (Onglyza)	Initial/MDD: 2.5-5mg PO QD	Tablet: 2.5mg, 5mg		N
Sitagliptin (Januvia)	Initial/MDD: 100mg PO QD	Tablet: 25mg, 50mg, 100mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
SGLT-2 INHIBITORS[1, 10]				
Canagliflozin (Invokana)	Initial: 100mg PO AM before first meal of the day MDD: 300mg/day	Tablet: 100mg, 300mg	**SGLT-2 inhibitors** • Deprescribe when possible • Increases insulin sensitivity • Dose reductions may be needed if used with sulfonylureas, insulin • Do not use if severe renal impairment (eGFR<45) or volume depletion • Adverse effects include genitourinary fungal infections, UTI, increased urination/thirst, hypotension, fractures • Nausea/vomiting should prompt suspicion of DKA • Expensive **Canagliflozin & Empagliflozin** • May slow progression of heart failure/ CKD • Can cause hypotension if used with loop diuretics **Canagliflozin** • Renal dose adjustments required • Drug interactions with common enzyme inducers (eg, rifampin, phenytoin, phenobarbital) • Increased risk of lower limb amputations; use with caution if PVD, diabetic foot ulcers, neuropathy; discontinue if infections, pain/ tenderness, or sores involving lower limbs • May cause hyperkalemia	Y
Dapagliflozin (Farxiga)	Initial: 5mg PO QAM MDD: 10mg/day	Tablet: 5mg, 10mg		Y
Empagliflozin (Jardiance)	Initial: 10mg PO QAM MDD: 25mg/day	Tablet: 10mg, 25mg		Y
Ertugliflozin (Steglatro)	Initial: 5mg PO QAM MDD: 15mg/day	Tablet: 5mg, 15mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
GLP-1 AGONISTS [1, 10]				
Dulaglutide (Trulicity)	Initial: 0.75mg SQ QW Max. weekly dose: 1.5mg/week	Solution for injection: 0.75mg/0.5ml, 1.5mg/0.5ml	**GLP-1 Agonists** • Deprescribe when possible • Increases insulin sensitivity • Hypoglycemia may occur if used with insulin or sulfonylureas • Caution if renal/hepatic impairment, history of pancreatitis • Slows gastric emptying; do not use if gastroparesis • GI side effects are common • Expensive **Exenatide & Liraglutide** • Caution if heart disease, gall bladder disease **Exenatide** • Do not use if severe renal impairment	N/A
Exenatide (Byetta, Bydureon)	Initial (IR): 5mcg SQ BID within 60 mins of AM/PM meals (give doses at least 6 hours apart) MDD (IR): 10mcg SQ BID Initial/Max. weekly dose (ER): 2mg SQ QW	Suspension for injection (ER): 2mg/0.85ml Solution for injection (IR): 5mcg/0.02ml, 10mcg/0.04ml		N/A
Liraglutide (Victoza)	Initial: 0.6mg SQ QD x 1 week, then titrated to response MDD: 1.8mg/day	Solution for injection: 18mg/3ml		N/A
Lixisenatide (Adlyxin)	Initial: 10mcg SQ QD before first meal of the day MDD: 20mcg/day	Solution for injection: 10mcg/0.2ml, 20mcg/0.2ml		N/A
Semaglutide (Ozempic)	Initial: 0.25mg SQ QW Max. weekly dose: 1mg/week	Solution for injection: 2mg/1.5ml		N/A

References

1. American Diabetes Association. Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42(Suppl. 1):S173–S181.
2. McCulloch, DK. Classification of diabetes mellitus and genetic diabetic syndromes. UpToDate. Waltham, MA: UpToDate Inc.; literature review current through May 2019.
3. Inzucchi, SE et al. Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults. UpToDate. Waltham, MA: UpToDate Inc.; literature review current through May 2019.
4. Hirsch, IB et al. Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis. UpToDate. Waltham, MA: UpToDate Inc.; literature review current through June 2019.
5. Makunts, T et al. Retrospective analysis reveals significant association of hypoglycemia with tramadol and methadone in contrast to other opioids. Scientific Reports. 2019;9(1):12490.
6. Fournier, J et al. Tramadol use and the risk of hospitalization for hypoglycemia in patients with Noncancer pain, JAMA Internal Med, 2015;175(2):186.
7. Flory, J et al. Methadone use and the risk of hypoglycemia for inpatients with cancer pain, J of Pain and Symptom Mgmt, article in press 2015.
8. Lee, SJ et al. Improving diabetes care for hospice patients. American Journal of Hospice & Palliative Medicine. 2016;33(6):517-519.
9. Gellar, AI et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. JAMA Internal Medicine. 2014;174(5):678-686.
10. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019.
11. Munshi, MN et al. Management of diabetes in long-term care and skilled nursing facilities: A position statement of the American Diabetes Association, Diabetes Care, 2016;39:308.
12. American Geriatrics Society 2019 Beers Criteria Update Expert Panel. American Geriatrics Society 2019 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019; 67(4):674-694.
13. Olivo, A. He lost his insurance and turned to a cheaper form of insulin. It was a fatal decision., The Washington Post, August 3rd 2019, accessed online at: https://www.washingtonpost.com/local/he-lost-his-insurance-and-turned-to-cheaper-form-of-insulin-it-was-a-fatal-decision/2019/08/02/106ee79a-b24d-11e9-8f6c-7828e68cb15f_story.html
14. Snouffer, E. Relion insulin dangerous for type 1 diabetes, diabetesvoice.org, August 7th 2019, accessed online at: https://diabetesvoice.org/en/diabetes-views/relion-insulin-dangerous-for-type-1-diabetes/
15. Cryer PE. Hypoglycemia in adults with diabetes mellitus. UpToDate. Waltham, MA: UpToDate Inc. Accessed on October 4, 2019.
16. Diabetes.org, accessed online March 2020 at: https://www.diabetes.org/diabetes/medication-management/blood-glucose-testing-and-control/hypoglycemia
17. Gonzalez, F et al. Fast Facts and Concepts #291: Hypoglycemia management in non-diabetic adults at the end of life.
18. Kwon, S et al. Glucocorticoid-induced hyperglycemia. The American Journal of the Medical Sciences. 2013;345(4):274-277.
19. Saag, KG et al. Major side effects of systemic glucocorticoids. UpToDate. Waltham, MA: UpToDate Inc.; literature review current through June 2019.
20. Angelo, M et al. An Approach to diabetes mellitus in hospice and palliative medicine. Journal of Palliative Medicine. 2011;41(1):83-87.
21. Centers for Medicare & Medicaid Services, 42CFR Part 418, Medicare Program; FY 2015 Hospice Wage Index and Payment Rate Update and Hospice Quality Reporting Requirements; 2014, available online at: https://www.federalregister.gov/documents/2014/05/08/2014-10505/medicare-program-fy-2015-hospice-wage-index-and-payment-rate-update-hospice-quality-reporting

Gout

DEFINITION

Gout is a disease caused by urate crystal deposits in joints, bones, and soft tissues. It can manifest as painful attacks of acute arthritis (or flares), chronic arthritis, or nephropathy, or tophi. [1, 2]

CAUSES

- Elevated serum urate concentrations (hyperuricemia) lead to the accumulation of monosodium urate crystals in synovial fluid within and around joints. [1, 2]
- Hyperuricemia is usually the result of biochemical over production or under excretion of uric acid, a metabolic waste product. [2, 3]
- Modifiable and non-modifiable risk factors increase gout risk (**Table 1**).

TABLE 1 – GOUT RISK FACTORS [1, 2, 4]

Modifiable	Non-modifiable
• Obesity (2x more likely than non-obese individuals) • Diets rich in meat and seafood • Alcohol use • Drinking sodas and fruit juices high in fructose or sucrose content • Hypertension • Chronic kidney disease • Recent surgery or trauma • Medications » Aspirin » Niacin » Thiazide or loop diuretics » Calcineurin inhibitors (eg, cyclosporine, tacrolimus) » Pancreatic enzymes (high-doses)	• Male gender (3x more likely than females) • Advanced age • Ethnicity (eg., Pacific Islanders) • Genetic predisposition (HGPRT enzyme deficiency)

HOW TO RECOGNIZE SYMPTOM [1, 2, 4]

- Appearance
  - » Gout flares typically present with localized:
    - ° Severe pain
    - ° Redness
    - ° Warmth
  - » With advanced disease, tophi (visible/palpable, non-tender collections of solid urate and accompanying inflammation / destruction to local connective tissue) are often present
- Location
  - » Flares usually involve a single joint (monoarticular), but can occasionally involve multiple joints (polyarticular).
  - » 80% of initial flares involve a single lower extremity joint, most often the base of the great toe. However, any joint, including ankles, knees, wrists, fingers, and elbows can be affected.
  - » Risk of polyarticular symptoms increases with persistent untreated gout.
- Timing
  - » Symptoms are most intense within 12 to 24 hours of onset.
  - » Onset is twice as likely to occur overnight between midnight and 8AM compared to waking hours.
- Findings
  - » Laboratory workup to support a gout diagnosis is not typically conducted in the hospice setting, but the following would otherwise be observed:
    - ° Hyperuricemia (serum urate > 6.8mg/dL)
    - ° Monosodium urate crystals in synovial fluid
    - ° White blood cell (WBC) counts in joint fluid ranging between 10-100k that are predominantly neutrophils
  - » A clinical diagnostic model assigning a points value to seven variables can be used to estimate the likelihood of gout, however the model heavily considers serum urate values that are not likely to be available in the hospice setting. [5]
    - ° Male sex (2 pts)
    - ° Patient-reported history of arthritis flare (2 pts)
    - ° Onset within one day (0.5 pts)
    - ° Joint redness (1 pt)

- First metatarsal phalangeal joint involvement (2.5 pt)
- HTN or ≥1 cardiovascular disease (1.5 pts)
- Serum urate >5.88mg/dL (3.5 pts)
- Total score (Probability): ≤4 (low), >4 to <8 (intermediate), ≥8 (high)

» Patients may experience fever

CLINICAL INSIGHTS

GENERAL

- While gout affects only a minority of Americans (~3%), it disproportionately affects elderly patients (~13% of patients > 80 years old).[2, 4]
- Non-pharmacologic measures to reduce gout are not always feasible in hospice patients, but can be considered.
  - » Weight reduction and limited alcohol consumption have been shown to reduce the risk of gout and gouty attacks.
  - » The degree of urate-lowering effects through dietary modifications may be insufficient to effectively lower serum urate in patients with persistent hyperuricemia, but avoidance of known dietary triggers may play a role in preventing gout flares.[2, 6]
- Unless essential for palliation of symptoms, attempt to deprescribe medications known to precipitate hyperuricemia/gouty attacks, such as thiazide and loop diuretics, niacin, cyclosporine, and tacrolimus.
- Hyperuricemia and gout do not contribute to the terminal prognosis of hospice patients and therefore gout treatments may not be part of the hospice plan of care. However, we recommend hospice coverage of gout treatments when a patient has a primary hospice diagnosis related to CKD/renal failure or if treating related conditions has the potential to affect gout symptoms (eg., use of loop diuretics in heart failure).

ACUTE TREATMENT

- The goal of therapy is prompt relief of pain and disability.[4, 7]
- Flares usually resolve within days to weeks, but to minimize discomfort and expedite symptom resolution anti-inflammatory agents should ideally be started within hours of symptom onset.[4, 7]
- Oral NSAIDs (effective in 90% of patients) and corticosteroids are preferred anti-inflammatory medications for treating acute gout attacks.[8] Colchicine is an alternative agent.[2, 7]
- Comorbidities (eg., renal impairment, heart disease, GERD, diabetes), avoiding potential drug interactions (eg., diminished response to ACE-inhibitors/ARBs with NSAID use), and drug costs should guide the choice of the anti-inflammatory agent to be used for acute gout attacks.[2–4, 7]
- Most oral NSAIDs are effective, but they should be used cautiously in patients with certain comorbidities (See Pain – Nociceptive / Tissue monograph for guidance with NSAID selection).[9]
  - » There is not yet consensus regarding efficacy or lack thereof with topical NSAIDs.
- Acute treatment can usually be stopped within two to three days of complete symptom resolution. Corticosteroids may need to be tapered over a longer period of time to prevent rebound attacks.[2, 7]
- Injectable corticosteroids may be necessary in patients unable to take oral medications.
- Combination therapy with intraarticular corticosteroids + one or two oral agents (colchicine + NSAID or oral steroid) may be necessary in severe cases.[7]
- Urate-lowering therapy fails to serve a benefit during gout flares, but it should be continued without interruption because intermittent treatment or discontinuation can lead to recurrent gout attacks.[7]

CHRONIC TREATMENT / SUPPRESSION

- Prior to hospice election, patients with a history of ≥2 flares/year have typically been prescribed chronic urate-lowering therapy with xanthine oxidase inhibitors (XOIs) or uricosuric agents to prevent recurrence.[2, 8, 9]
  - » Monotherapy with an XOI or probenecid is typically sufficient although combination therapy is occasionally used in refractory cases.
- There is minimal guidance regarding prescribing and deprescribing of urate-lowering therapy in hospice patients.

  - » For patients already receiving therapy, continuing it is reasonable because discontinuation may increase risk of painful acute attacks.[7]
  - » For patients with new onset acute gout attack, we recommend against commencing therapy because initiating treatment can precipitate attacks in the short term and although most patients with an acute attack would typically have another attack within two years, this timeframe substantially exceeds the life expectancy of hospice patients.[2, 4]

- Interestingly, dose of losartan of 50mg or less have modest uric-acid lowering effects and may be used preferentially if antihypertensives/angiotensin-receptor blockers are otherwise indicated in patients with gout.[10]

DRUG INFORMATION

ACUTE TREATMENT

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NSAIDS[2, 3, 7, 9, 11]				
Celecoxib (Celebrex)	Initial: 200mg PO BID MDD: 400mg/day	Capsule: 50mg, 100mg, 200mg, 400mg	**NSAIDs** • Initiate within 48 hours of flare onset and continue for ≥2-3 days after symptom resolution for optimal results • Usual duration is 5 to 7 days • May cause GI upset; take with food or milk • Avoid if heart failure or GFR <30 **Indomethacin** • Avoid in elderly due to increased risk for GI bleeding, ulcers, kidney injury, adverse CNS effects **Naproxen** • 275mg naproxen sodium = 250mg naproxen • DR tablets not recommended due to delayed absorption **Sulindac** • Potentially less renal toxicity vs. other NSAIDs **Diclofenac** • May cause hepatoxicity **Celecoxib** • Less evidence supporting use compared to other NSAIDs • Caution in patients with sulfa allergy • Expensive **Meloxicam** • Capsules and ODT expensive	Y
Diclofenac sodium (Voltaren, Voltaren XR) and Diclofenac potassium (Cataflam)	Initial (IR, DR): 50mg PO BID MDD: 100mg/day	Tablet (DR)*: 25mg, 50mg, 75mg Tablet (ER)*: 100mg Tablet (IR): 50mg		Y/N*
Ibuprofen (Advil, Motrin)	Initial: 800mg PO TID MDD: 3,200mg/day	Capsule: 200mg Chewable tablet: 100mg Oral suspension: 100mg/5ml, 40mg/ml Tablet: 200mg, 400mg, 600mg, 800mg		Y
Indomethacin (Indocin)	Initial: 50mg PO TID MDD: 200mg/day	Capsule: 25mg, 50mg Capsule (ER)*: 75mg Oral suspension: 25mg/5ml Suppository: 50mg		Y/N*
Meloxicam (Mobic, Qmiiz, Vivlodex)	Initial: 15mg PO QD MDD: 15mg/day	Capsule: 5mg, 10mg Oral disintegrating tablet (ODT): 7.5mg, 15mg Tablet: 7.5mg, 15mg		Y
Naproxen (Aleve, Naprosyn)	Initial (IR): 500mg PO BID Alternate: 750mg x 1 dose, then 250mg every 8 hours until attack has subsided MDD: 1,000mg/day	Capsule: 220mg Oral suspension: 125mg/5ml Tablet: 220mg, 250mg, 375mg, 500mg Tablet (DR)*: 375mg, 500mg Tablet (ER)*: 375mg, 500mg, 750mg		Y/N*
Sulindac (Clinoril)	Initial: 200mg PO BID MDD: 400mg/day	Tablet: 150mg, 200mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CORTICOSTEROIDS[2, 3, 7, 9, 11]				
Methylprednisolone (Medrol, Solu-Medrol, Depo-Medrol)	Initial (PO): 24-32mg PO daily in 1 to 2 divided doses until symptom improvement then taper Initial (IM; acetate or succinate): 40-60mg IM x 1 dose; may repeat once or twice with 48 hours between doses PRN MDD (PO): 120mg/day MDD (IM): 60mg as single dose	Solution for injection (succinate): 40mg, 125mg, 500mg, 1000mg, 2g Suspension for injection (acetate): 20mg/ml, 40mg/ml, 80mg/ml Tablet: 2mg, 4mg, 8mg, 16mg, 32mg	**Corticosteroids** • Prednisone is the prototypical corticosteroid for gout management • Preferred treatment if renal impairment • Use with caution in diabetic patients due to hyperglycemic effects • Use with caution in patients with recent GI bleed • Take with food or milk to minimize risk of GI upset • Give last dose by 2pm to avoid steroid-induced insomnia • Other possible adverse effects include mood changes and fluid retention • 7-10 day minimum taper recommended after symptoms improve, but longer tapers may be necessary if recurrent flares	Y
Prednisolone (Millipred, Orapred)	Initial (PO): 0.5mg/kg/day for 5 to 10 days or 30-40mg/day in 1 to 2 divided doses until symptom improvement then taper MDD: 80mg/day	Oral disintegrating tablet (ODT)*: 10mg,15mg, 30mg Oral Solution: 5mg/5ml, 10mg/5ml, 15mg/5ml, 20mg/5ml, 25mg/5ml Tablet: 5mg		Y/N*
Prednisone (Deltasone)	Initial (PO): 0.5mg/kg/day for 5 to 10 days or 30-40mg/day in 1 to 2 divided doses until symptom improvement then taper MDD: 80mg/day	Oral solution: 1mg/ml, 5mg/ml Tablet: 1mg, 2.5mg, 5mg, 10mg, 20mg, 50mg		Y
Triamcinolone (Kenalog)	Initial: 40-60mg IM x 1 dose; may repeat once or twice with 48 hours between doses PRN MDD: 60mg as single dose	Suspension for injection: 10mg/ml, 40mg/ml, 80mg/ml		-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIGOUT AGENT[2, 3, 7, 9, 11]				
Colchicine (Colcrys, Gloperba, Mitigare)	**Treatment** Initial (Day 1): 1.2mg PO at first sign of flare, then 0.6mg PO 1 hour later OR 0.6mg PO TID MDD (Day 1): 1.8mg/day Initial (Day 2 +): 0.6mg PO QD until flare resolves; d/c 2-3 days after flare resolution MDD (Day 2 +): 1.2mg/day **Prophylaxis** Initial: 0.3mg-0.6mg PO QD-BID MDD: 1.2mg/day (0.6mg if ≥70 y.o.)	Capsule: 0.6mg Oral solution: 0.6mg/5ml Tablet: 0.6mg	• Indicated for flare treatment and prophylaxis during initiation of urate-lowering therapy • Most effective when taken within 24 hours of flare onset • Reserve for patients who cannot take NSAIDs or corticosteroids • Benefits of low-doses may be comparable to high-dose regimens • GI side effects are common and may indicate toxicity (esp. in older patients) • Many drug interactions • Avoid grapefruit juice • Requires renal/hepatic dose adjustments; avoid if severe impairment • Expensive	Y

GOUT PROPHYLAXIS (URATE-LOWERING THERAPY)

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
XANTHINE OXIDASE INHIBITORS (XOIS) [2, 3, 7, 9, 11]				
Allopurinol (Zyloprim)	Initial: 100mg PO QD Titrated by 100mg every 2 to 4 weeks as necessary MDD: 800mg/day	Tablet: 100mg, 300mg	• First line urate-lowering therapy • Administer after meals • Typically well-tolerated, but doses may be divided BID-TID to improve GI tolerability • Requires renal dose adjustment if CrCl ≤60ml/min • Also indicated to prevent kidney stone formation and tumor lysis syndrome	Y
Febuxostat (Uloric)	Initial: 40mg PO QD MDD: 120mg/day(40mg/day if CrCl<30ml/min)	Tablet: 40mg, 80mg	• Caution if history of hypersensitivity to allopurinol or severe renal/hepatic impairment • Expensive	Y
URICOSURIC AGENT [2, 3, 7, 9, 11]				
Probenecid	Initial: 250mg PO BID for 1 week, then increase to 500mg PO BID May titrate by 500mg every 4 weeks MDD: 2,000mg/day	Tablet: 500mg	• May reduce dose by 500mg every 6 months if no attacks after 6 months • Avoid if GFR<50ml/min due to reduced efficacy • Take with food to minimize GI upset • Increased risk of urolithiasis • Many drug interactions	Y

References

1. Becker MA, et al. Pathophysiology of Gout. UptoDate. Waltham, MA: UptoDate Inc.; 2019.
2. Fravel MA, et al. Chapter 74. Gout and Hyperuricemia. Pharmacotherapy: A Pathophysiologic Approach, 9e. Eds. Joseph T. DiPiro, et al. New York, NY: McGraw-Hill, 2014.
3. Pittman JR, et al. Diagnosis and Management of Gout. American Family Physician. 1999;59(7): 1799-1806.
4. Becker MA, et al. Clinical Manifestations of Gout. UptoDate. Waltham, MA: UptoDate Inc.; 2019.
5. Janssens HJ, et al. A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis. Archives of Internal Medicine. 2010;170(13):1120.
6. Khanna D, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care & Research. 2012;64(10):1431–1446.
7. Becker MA, et al. Treatment of Gout Flares. UptoDate. Waltham, MA: UptoDate Inc.; 2019.
8. Schumacher, H. Ralph, and Lan X. Chen.. "Gout and other crystal-associated arthropathies." Harrison's Principles of Internal Medicine, 20e Eds. J. Larry Jameson, et al. New York, NY: McGraw-Hill,2018.
9. Schumacher Jr HR, et al. The practical management of gout. Cleveland Clinic Journal of Medicine. 2008;75(suppl 5):S22-S25.
10. Würzner G, et al. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. Journal of hypertension. 2001;19(10):1855-1860.
11. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019.

Hepatic Encephalopathy

DEFINITION

A brain dysfunction caused by liver insufficiency and/or portal-systemic shunt that manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alteration to coma [19]

CAUSES

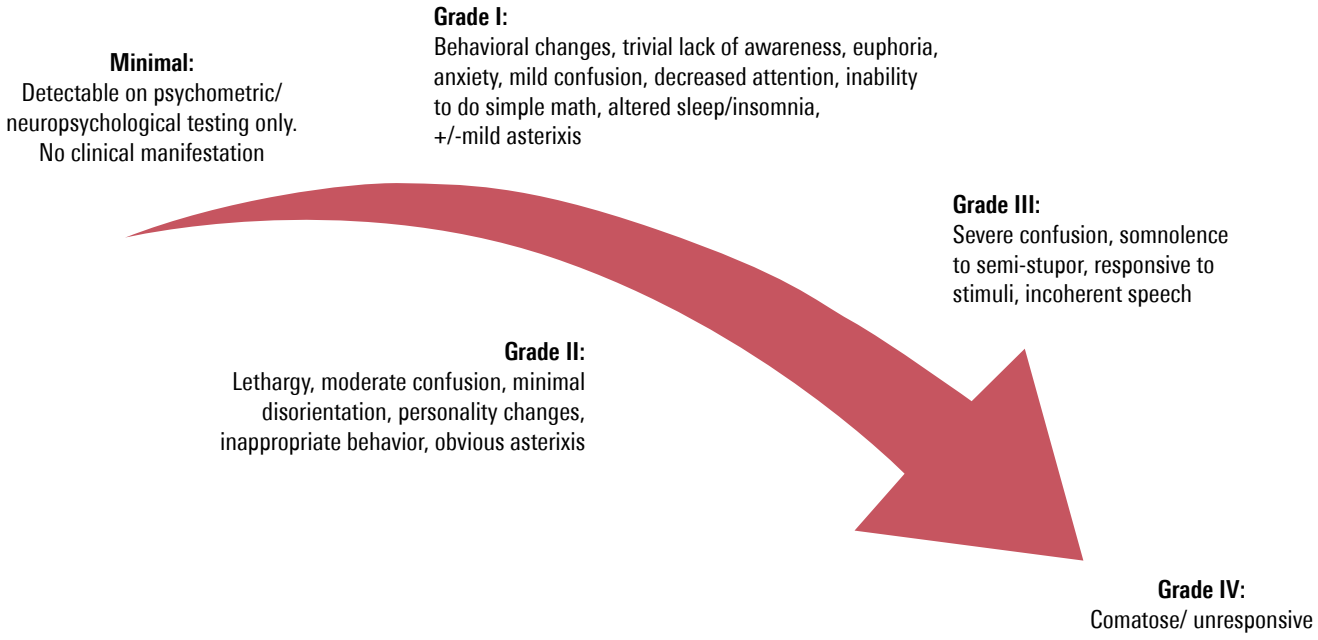
- By definition, liver disease is the underlying cause of hepatic encephalopathy (HE), which can be characterized depending on the type of liver impairment. [2, 3]
  - » Type A: acute liver failure
  - » Type B: portal-systemic bypass with no intrinsic hepatocellular disease
  - » Type C: cirrhosis with portal hypertension or systemic shunting
    - ° Most common type encountered in the hospice setting.
    - ° Creation of portosystemic shunts, which can be used to treat portal hypertension is associated with a 30% chance of developing HE. [18]
- Common precipitating factors of hepatic encephalopathy are infection, alcohol use, medications (benzodiazepines, opioids, antidepressants, antipsychotics and other sedatives), gastrointestinal bleeding, excessive dietary protein, constipation, dehydration, renal failure, hypokalemia, hyponatremia, hypoglycemia, anemia, and hypoxia [2 – 3, 5, 18]
- Although hyperammonemia due to liver impairment is the most extensively characterized cause, HE development may reflect any combination of metabolic encephalopathy (ie, hyperammonemia and other nitrogenous substances) and/or atrophy, swelling or hypoperfusion of the brain. [1, 4 – 5, 18]
- Hyperammonemia negatively affects the brain in several ways, including: [18]
  - » Impaired neurotransmission – The loss of NMDA receptors observed in studies of HE patients could alter neuronal excitability in a way that contributes to neurologic dysfunction. Altered dopaminergic transmission plays a role in the development of extrapyramidal symptoms, which are commonly seen with HE.
  - » Increased permeability of the blood brain barrier, allowing more toxins to cross
  - » Impaired cerebral glucose metabolism, starving the brain of energy
  - » Oxidative stress, which is thought to cause astrocyte swelling and impaired function as well as post-synaptic protein synthesis, causing altered learning and memory consolidation
- Cachexia can contribute to HE development, as muscle is another site besides the liver for ammonia removal. [18]
- Other diseases that can contribute to HE include cystic fibrosis, alpha-1-antitypsin deficiency, and Wilson disease [1]

HOW TO RECOGNIZE SYMPTOM

- HE should be considered when altered mental status is present in the context of known liver disease
- HE is a diagnosis of exclusion. Metabolic disorders, infection, intracranial lesions, drug-induced cognitive impairment, alcohol / illicit drug use or withdrawal, and cerebrovascular events should be considered in the differential diagnosis.
- HE can follow different time courses:
  - » Episodic
  - » Recurrent – multiple HE occurrences within a 6-month period
  - » Persistent – HE always present
- Alterations of consciousness may undergo spontaneous fluctuations and can be influenced by concurrent clinical factors, such as infection, hypoxemia, GI hemorrhage, or electrolyte disturbances [2]
- Chronic (type C HE) is characterized by impaired neurological function, personality / mood changes, reduced intellectual capacity, abnormal muscle tone and tremor [20]
- HE manifestations are not always obvious (ie, covert HE) and there are multiple tools to assist with detection [19]
- Psychometric and neurophysiological tests to detect covert HE are rarely employed in the hospice setting.
- Asterixis ("flapping tremor") is common is the early to middle stages of HE [19]
- Non-comatose patients with HE exhibit motor system abnormalities including hypertonia, hyperreflexia and a positive Babinski sign [19]

- Extrapyramidal symptoms (EPS), such as hypomimia (masked facies), muscle rigidity, brady/hypo/dyskinesia, monotone or slowed speech, and tremor are often seen with HE [19]
- The West Haven Criteria are used to grade the severity of HE (**Figure 1**):

FIGURE 1 – WEST HAVEN CRITERIA FOR HEPATIC ENCEPHALOPATHY



- HE is also characterized as covert (minimal through Grade I) and overt (Grade II or higher)
- HE descriptions can be supplemented with the level of consciousness as described by the Glasgow Coma Scale (**Table 2**)

TABLE 1 [4] – GLASGOW COMA SCALE

EYES OPEN		BEST MOTOR RESPONSE		BEST VERBAL RESPONSE	
Spontaneously	4	Obeys verbal orders	6	Oriented, conversant	5
To command	3	Localizes painful stimuli	5	Disoriented, conversant	4
To pain	2	Painful stimulus, flexion	3	Inappropriate words	3
No response	1	Painful stimulus, extension	2	Inappropriate sounds	2
		No response	1	No response	1

Severe encephalopathy is defined as a score <12

CLINICAL INSIGHTS

- HE is associated with a poor prognosis (1-yr survival of 40%)[4]
- Nearly all instances of type C HE can be traced to one or more precipitating factors. Correction of the precipitating factor alone can resolve nearly 90% of overt HE episodes.[19]
- The first step in treating HE is to identify and correct precipitating factors, including infections, sedative medication use, dehydration, acid-base and electrolyte disturbances, and constipation. If none are identified, consider drug therapy[5]
- The risks and benefits of benzodiazepine use in patients with HE should be carefully weighed, considering goals of care, as they commonly precipitate HE.
- Flumazenil, a benzodiazepine antagonist, may be considered in select cases where benzodiazepine use is suspected as a precipitating factor of HE[4, 5]
- Blood ammonia levels alone do not add value to prognostication or diagnosing / staging HE[19]
- Once initiated, drug therapy to treat HE is typically continued indefinitely, unless a precipitating factor is found and corrected[19]
- Lactulose, which lowers blood ammonia levels, is the drug of choice for HE. Questions regarding the superiority of lactulose over antibiotics have been raised, but there is not sufficient evidence to change current treatment recommendations[1]
- If lactulose is ineffective, precipitating factors and alternate causes of brain impairment may have been missed and should be re-addressed[19]
- Non-compliance and/or inadequate dose titration of lactulose are common reasons for treatment failure.
- Rifaximin should be reserved for patients who fail to respond or have intolerance to lactulose[17]
- There is no solid evidence that supports the use of monotherapy with rifaximin for HE[19]
- In some cases duplicate therapy with lactulose and other agents may be warranted.
- Rifaximin is the most effective choice to add to lactulose for secondary HE prevention.[19] High cost (up to $35 per 550mg tablet) may affect its use in the hospice setting.
- When considering both cost and efficacy, pharmacoeconomic cost-effective analyses favor lactulose-based treatments[19]
- Historically, other antibiotics besides rifaximin, such as neomycin and metronidazole have been used to treat HE. They have fallen out of favor in the non-hospice population because of the potential for adverse effects with long-term use. This may be of limited relevance in the terminally ill population.
- Dietary considerations[19]:
  - Consultation with a dietician can be beneficial
  - Both inadequate and excessive protein consumption can cause or worsen HE. Protein intake of 1.2-1.5 g/kg/day and energy intake of 35-40 kcal/kg of ideal body weight are recommended if possible.[3]
  - Small, evenly distributed meals during the day and an evening snack are preferred over large meals and periods of fasting[19]
  - Milk or vegetable proteins are preferred
  - Branched chain amino acid (BCAA) supplementation may be beneficial
  - Glucose should not be the only source of calories.
  - Multivitamins are commonly recommended, but their use is not backed by quality evidence
  - Continued alcohol use in the ESLD population is common and can limit use of metronidazole as HE treatment (disulfiram reaction).

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
NON-ABSORBABLE DISACCHARIDES				
Lactulose (Enulose) [4, 6]	Initial (oral): 30-45ml (20-30g) every hr to induce rapid laxation; then reduce to TID/QID to produce 2-3 loose stools per day Initial (enema): retain for 30-60 min, repeat every 4-6hrs MDD: 240ml/day	Enema: combine 300ml (200g) of solution and dilute with 700ml of water or NS Oral solution: 10g/15ml	• Onset of action at least 24-48 hours • Adjust dose every 1-2 days to produce 2-3 soft stools per day, avoiding diarrhea • Overuse of lactulose can cause aspiration, dehydration, hypernatremia, electrolyte imbalances due to diarrhea and severe perianal skin irritation [19] • Does not increase blood glucose • Can administer as a rectal enema	-
ANTIBIOTICS				
Metronidazole (Flagyl) [4, 10]	Initial: 250mg PO BID MDD: 1g/day	Capsule: 375mg Oral suspension: 50mg/ml (crush twenty-four 250mg tablets; add ~120ml of vehicle) Tablet: 250mg, 500mg	• Take IR dosage forms with food to minimize stomach upset. • Contraindicated with use of disulfiram within 2 weeks, use of alcohol or propylene glycol products during therapy and for three days after. • Neurotoxicity is a potential adverse effect that may limit long-term use	Y
Neomycin (Neo-Fradin) [4, 8, 9]	Initial: 3-6g daily divided q4-6hr for 1-2 weeks MDD: 12g/day	Oral solution: 25mg/ml Tablet: 500mg	• Contraindicated for patients with inflammatory or ulcerative GI disease • Black box warnings: nephrotoxicity, neuromuscular blockade and respiratory paralysis, and neurotoxicity • 97% of oral doses act locally in the gut. The remaining 3% can accumulate in the kidneys or ears, resulting in renal / ototoxicity. As such, treatment duration is typically limited to 2 weeks or less. • Dose adjust for renal impairment	-
Rifaximin (Xifaxan) [7]	Initial: 400mg q8hr for 5-10 days Recurrence: 550mg BID for 6 months MDD: 1,100mg/day	Oral suspension: 20mg/ml (crush six 200mg tablets, add ~60ml Ora-Sweet) Tablet: 200mg, 550mg	• Frequency of ADRs are higher when treating HE • Medication acts locally in the gut • Expensive	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
METABOLIC AMMONIA SCAVENGERS				
Glycerol phenylbutyrate (Ravicti) [3, 15]	Initial: 6ml PO BID	Oral solution: 1.1g/ml	• May reduce number of HE episodes and hospitalizations [19] • Administer with food • May be administered via NG tube • Very expensive (more than $1,000 per day) and limited distribution (specialty drug)	-
L-ornithine L-aspartate [3, 5]	Initial: 20g IV infusion over 4hrs Daily MDD: 40g/day	Solution for injection: 500mg/ml	• May improve symptoms of encephalopathy • Adjunctive treatment for nonresponsive patients • Oral supplements are ineffective [19]	-
SUPPLEMENTS				
Acetyl-L-carnitine [3, 16]	Initial: 2g PO BID for 90 days	Capsule: 500mg	• Associated with improved fatigue severity in patients with mild or moderate hepatic encephalopathy • Nausea, vomiting, abdominal cramps, diarrhea, and a "fishy" body odor can occur with doses of about 3g/day	Y
Zinc [4]	Initial (zinc sulfate or acetate): 600mg/day Initial (zinc L-Carnosine/ polaprezinc): 225mg/day	Capsule (zinc acetate): 25mg, 50mg Capsule (zinc sulfate): 225mg	• Zinc deficiency may cause or contribute to HE; supplementation is reasonable if a known deficiency exists • Administer on an empty stomach • May reduce the absorption of fluoroquinolone or tetracycline type antibiotics. • May improve psychomotor function scores	N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MISCELLANEOUS				
Bromocriptine (Parlodel) [4, 13]	Initial: 30mg PO BID MDD: 100mg/day	Capsule: 5mg Tablet: 2.5mg	• Indicated for the treatment of chronic encephalopathy in patients unresponsive to other therapies • May result in elevated prolactin levels • Administer with food • Most common side effects are dizziness, fatigue, GI upset, and weakness • Monitor for drug interactions	Y
Flumazenil (Romazicon) [4, 11, 12]	Initial: 1mg bolus IV MDD: 5mg/day	Solution for injection: 0.5mg/5ml, 1mg/10ml	• Uncommonly used • Transiently improves mental status without improvement on recovery or mortality [19] • Indicated for patients with HE and suspected benzodiazepine intake • Black Box Warning: increase risk of seizures • Most common side effect is vomiting • Onset of action within 1-2 minutes, 80% response in 3 minutes	-

References

1. Lexicomp [Internet]. Lexi-Comp, Inc. c 1977-2016. Hepatic Encephalopathy; [Accessed 2016 Sep 2016].
2. UpToDate [Internet]. UpToDate, Inc. c2016. Hepatic encephalopathy in adults: Clinical Manifestations and diagnosis; Topic 1237, Version 27.0; [Updated Sep 2015; Accessed Sep 26, 2016].
3. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 116905, Hepatic encephalopathy; [updated 2016 Jul 08, Accessed Sep 26, 2016].
4. Blei A, Cordoba J. Hepatic Encephalopathy. The American Journal of Gastroenterology 96, 1968-1976 (July 2001) | doi:10.1111/j.1572-0241.2001.03964.x; [Accessed Sep 26, 2016].
5. Keen J. Oxford Textbook of Palliative Medicine (5 edition).Oxford University Press; Mar 2015. Section 10.2.5, Jaundice, ascites, and encephalopathy; [Accessed Sep 26, 2016]. Pages 877-880.
6. Lexicomp [internet]. Wolters Kluwer Clinical Drug Information, Inc. c2016. Lactulose; [updated Sep 9, 2016; Accessed Sep 27, 2016].
7. Lexicomp [internet]. Wolters Kluwer Clinical Drug Information, Inc. c2016. Rifaximin; [updated Sep 22, 2016; Accessed Sep 27, 2016].
8. Lexicomp [internet]. Wolters Kluwer Clinical Drug Information, Inc. c2016. Neomycin [updated Aug 24, 2016; Accessed Sep 27, 2016].
9. Truven Health Analytics. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 908278, Neomycin Sulfate; [updated 2015 Dec 22, Accessed Sep 27, 2016].
10. Lexicomp [internet]. Wolters Kluwer Clinical Drug Information, Inc. c2016. Metronidazole [updated Sep 27, 2016; Accessed Sep 27, 2016].
11. Lexicomp [internet]. Wolters Kluwer Clinical Drug Information, Inc. c2016. Flumazenil [updated Sep 15, 2016; Accessed Sep 27, 2016].
12. Truven Health Analytics. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 233412, Flumazenil; [updated 2016 Jan 20, Accessed 2016 Sep 27].
13. Lexicomp [internet]. Wolters Kluwer Clinical Drug Information, Inc. c2016. Bromocriptine [upadated Sep 16, 2016;Accessed Sep 27 2016].
14. Lexicomp [internet]. Wolters Kluwer Clinical Drug Information, Inc. c2016. Zinc Acetate [updated Aug 15, 2016, Accessed Sep 28, 2016].
15. Lexicomp [internet]. Wolters Kluwer Clinical Drug Information, Inc. c2016. Glycerol Phenylbutyrate [updated Aug 2, 2016; Accessed Sep 28, 2016].
16. Lexicomp [internet]. Wolters Kluwer Clinical Drug Information, Inc. c2016. L-Carnitine [Accessed Sep 28, 2016].
17. Jawaro, T. et al. Management of Hepatic Encephalopathy: A Primer, Annals of Pharmacotherapy, 2016 50:7;569-77.
18. Ferenci, P. et al. Hepatic encephalopathy: Pathogenesis, UpToDate, Accessed online Nov. 2016.
19. Vilstrup et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, Hepatology, 2014;60:715-35.
20. Jayakumar, A. Neuroinflammation in hepatic encephalopathy: Mechanical aspects, J of Clin Experim Hepatol, 2015;5(S1): S21-28.

Malodorous Wounds

DEFINITION

A skin lesion with ulcerations and necrosis that may have a purulent odor and exudates.

CAUSES

- Causes of odor
  - » Infection – metabolism of devitalized tissue by both anaerobic (primary) and aerobic bacteria produces a smell likened to that of rotting flesh
  - » Saturation of dressings with both bacterial and wound byproducts, including exudate, blood and pieces of necrotic flesh
  - » Fistula formation into a body cavity can increase odor and exudate
- Causes of wounds are many and include:
  - » Fungating lesions – infiltration and proliferation of malignant cells into the skin and support vasculature; most commonly occur with:
    - ° Breast cancer (most common)
    - ° Melanoma
    - ° Lymphoma
    - ° Lung cancers
    - ° Stomach cancer
    - ° Head / neck cancer
    - ° Uterine cancer
    - ° Kidney cancer
    - ° Ovarian cancer
    - ° Colon cancer
    - ° Bladder cancer
  - » Ulcers (eg, venous, pressure)
  - » Trauma
  - » Burns
  - » Diabetes

HOW TO RECOGNIZE SYMPTOM

- Malodor from wound that may be described as sweet, pungent, foul, strong, fecal or musty
  - » A sweet odor may indicate Pseudomonas infection
  - » A strong, pungent odor accompanied by necrosis or layering of the skin may indicate Clostridium infection, which can be life-threatening
- Exudates from skin lesion
- Fungating lesions growth involves two process, which may occur concurrently or alone:
  - » Ulcerative – crater-like wounds
  - » Proliferative – often described as fungus-like or cauliflower-like in appearance

CLINICAL INSIGHTS

- Fungating/malodorous wounds have a significant psychological impact on the patient, family, and healthcare team. The patient may experience separation from family and friends, and may face revulsion by caretakers.
- Pain, bleeding and itching may accompany malodorous wounds
  - » Avoid adherent dressings
  - » Consider planning additional rescue doses of analgesic prior to dressing changes
- Proper wound care can improve control of odor and patient satisfaction, even if the lesion is deteriorating.
  - » Debridement with enzymatic products should be considered to eliminate necrotic tissue
  - » Cleanse with irrigation thoroughly at each dressing change and before each administration of a topical product
- Malodorous wounds can stimulate the gag reflex and cause vomiting
- Non-pharmacological measures should be considered, including:
  - » Dispose of soiled dressings away from the patient
  - » Agents to mask odor, such as perfumes or essential oils (esp. during dressing changes)
  - » Specialized air filters or deodorizers
  - » Colostomy bags can be used for fistulae
  - » Baskets of cat litter or charcoal placed in the room
  - » Baking soda applied between dressing layers
- Metronidazole, either topically or systemically is the drug of choice for wound odor
- Systemic treatment with other antibiotics may be considered if there is evidence of clinical infection, rather than colonization
  - » Avoid overuse due to increased risk of overgrowth of resistant organisms and drug-induced adverse effects including nausea, vomiting and diarrhea

  - » May be of limited effectiveness, especially if circulation is reduced in proximity to the wound

- Silver dressings are antiseptic and may be beneficial as adjunct therapy, but are expensive
- Activated charcoal dressings may also be beneficial to isolate the odor
  - » Require a perfect seal around the wound for efficacy
  - » Can be inactivated by excessive wound exudate; use only in wounds with minimal exudate
  - » Only effective for a few hours
  - » Expensive
- Moh's paste (a zinc-containing compounded product) is potentially beneficial for odorous bleeding wounds
- Sugar paste may be beneficial
  - » Not commercially available; must be compounded.
  - » Absorbs fluids needed for bacterial growth
  - » Potentially inconvenient due to short duration of action; requires a thick layer be applied two or more times per day

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTIBIOTICS				
Metronidazole (MetroCream, Metrogel, MetroLotion, Noritate, Nuvessa, Rosadan, Vandazole)	Initial (Topical): Apply to wound QD-TID (use 1/8 inch thick layer for commercially available preparations) Initial (oral): 250-500mg PO Q8 hours x 5 days, then once daily Initial (rectal): 500mg PR BID x 5 days, then once daily MDD (topical): not established for this indication MDD (oral): 2,000mg/day	Capsule: 375mg Compounded solution: 0.5%, 1% Cream: 0.75%, 1% Gel: 0.75%, 1%, 1.3% Kit: 0.75% Lotion: 0.75% Tablet: 250mg, 500mg	• Drug of choice for wound odor • Solution may be compounded by crushing metronidazole tablets in sterile water • Compounded solution can be used as a wound irrigant or gauze can be soaked and packed into wound cavities • May take 3-7 days for odor to be eradicated • For wounds with heavy exudate, powder or crushed tablets are preferred • For dry wounds, gels, creams or lotions are preferred • Can be ineffective in wounds that are too moist or too dry • Avoid use in conjunction with other topical products that may dilute and reduce effectiveness • Alcohol use should be avoided due to disulfiram reaction • Peripheral neuropathy is a possible adverse effect with oral use; consider lower doses or avoiding in patients with existing disease • Commercially available topical products are expensive	-
Silver Sulfadiazine (Silvadene, SSD, Thermazine)	Initial: Apply cream in 1/16-inch layer topically once or twice daily MDD: Patient specific	Cream: 1%	• Shown to be beneficial for controlling odors of superficial wounds • May cause itching or skin irritation • May hasten wound healing • Contraindicated with sulfonamide allergy • Potential for cross-reactivity if allergy to other chemical similarities including sulfonylureas, carbonic anhydrase inhibitors, thiazides and loop diuretics	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTISEPTICS				
Cadexomer Iodine (Iodosorb)	Initial: apply 1/8 to ¼ inch layer to sterile gauze, then place onto clean wound. Change when gel changes color from brown to yellow/ grey, typically about 3 times per week. Remove with irrigation prior to reapplying.	Gel: 0.9%	• Preferred form of iodine for wound odor • Removes slough • Absorbs exudate • Maintains a moist wound environment • Inhibits and disrupts biofilms • Burning with application is a possible side effect	-
Leptospermum Honey (Medihoney)	Topical: with dressing changes	Dressing: 100% Leptospermum Honey	• Labeled uses included diabetic foot ulcers, leg ulcers, pressure ulcers (stages I-IV), burns (1st and 2nd degree), donor sites, and traumatic or surgical wounds • Can be applied either directly to wound or to primary dressing • Antimicrobial, absorbent and debriding effects attributed to acidic pH, hydrogen peroxide formation and high osmolality • Potentially difficult to apply and requires use of absorbent secondary dressing; avoid in wounds that are too moist • Do not substitute food grade honey, which may contain spores and other contaminates	-
Benzalkonium chloride (Zephiran Chloride)	Initial: 1:3,000 to 1:20,000 concentration topically twice daily MDD: Patient specific	Pledgets: 0.13% Tincture: 0.13% Topical solution: 0.13%, 17%, 50%	• Antiseptic cleanser used for external wounds • Limited anecdotal evidence to support use *(Continued on next page)*	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTISEPTICS (CONTINUED)				
Sodium Hypochlorite (Dakin's Solution, Di-Dak-Sol, H-Chlor 12, HySept)	Initial: Cleanse wound once or twice daily MDD: Patient specific	Topical solution: 0.0125%, 0.125%, 0.25%, 0.5%	• Protect the skin around the wound with a petrolatum barrier prior to irrigating with Dakin's • May be used to irrigate the wound directly or to soak dressings and bandages before application • Redness, irritation, swelling, and pain may occur • Potential for confusion exists with available strengths and product labeling: full strength = 0.5%, half strength = 0.25%, quarter strength = 0.125% • May consider diluting to 0.025% as studies have suggested higher concentrations may be harmful for wound healing • Limited anecdotal evidence to support use	-
ENZYMATIC DEBRIDING AGENTS				
Collagenase (Santyl)	Topical: Apply to wound topically once daily or more frequently if necessitated by soiled dressings MDD: Patient specific	Ointment: 250units/gram	• Debriding agent • Expensive	-
Trypsin, Balsam of Peru, Castor Oil (Granulex, Vasolex, Xenaderm)	Topical: Apply to wound topically a minimum of twice daily or as often as necessary MDD: Patient Specific	Ointment: Trypsin 90 USP, balsam Peru 87mg, and castor oil 788mg per gram Spray: Trypsin 0.1mg, balsam Peru 72.5mg, and castor oil 650mg per gram, Trypsin 0.12mg, balsam Peru 87mg, and castor oil 788mg per gram	• Debriding agent • Less expensive, but less effective than collagenase; reserve use for stage 1-2 decubiti	-
OTHER				
Chlorophyllin Copper Complex (Chloresium, Derifil, Ennds, Innerfresh Pro, Nullo, Pals)	Initial: 100mg PO twice daily MDD: 800mg/day	Tablet: 10mg, 20mg, 100mg	• Onset of action is generally 4-5 days • May titrate up weekly as necessary • Also used to control fecal odors in colostomy or ileostomy • Limited anecdotal evidence to support use	Y

References

- Alexander, S. Malignant fungating wounds: managing malodour and exudate, Journal of Wound Care, Vol. 18, No. 9 (2009).
- Bergstrom, K. Assessment and Management of Fungating Wounds, Journal of Wound, Ostomy and Continence Nursing Society, 2011; 38(1):31-37.
- Chai, E. et al. Geriatric Palliative Care – A Practical Guide for Clinicians, 2014, pp. 311-313.
- Fine, P. The Hospice Companion, 2nd ed. 2012, pp. 66.
- Hanks, G. et al. Oxford Textbook of Palliative Medicine, 4th ed. 2010, pp. 544,963-71.
- Kakimoto, M. et al. A chemical technique for bleeding from malignant wounds, Journal of Palliative Medicine, Vol. 13, No. 1, 2010.
- Langemo, D. et al. Managing Fungating Wounds, Advances in Skin and Wound Care, Vol. 20 No. 6.
- Lexicomp Online®, Hudson, Ohio: Lexi-Comp, Inc.; June, 2015.
- Lipsky, B. et al. Topical Antimicrobial Therapy for Treating Chronic Wounds, Clinical Infectious Diseases, 2009; 49:1541-9.
- Memedio da Costa Santos, C. et al. A systematic review of topical treatments to control the odor of malignant fungating wounds, J. Pain and Symptom Management, 2010 Vol 39 No.6 2010
- Patel, B. et al. Managing Wound Odor #218, Journal of Palliative Medicine, 13(10):1286-7, 2010 Oct.
- Regnard, C. et al. A Guide to Symptom Relief in Palliative Care, 6th ed. pp. 149-156.
- Seaman, S. Management of Malignant Fungating Wounds in Advanced Cancer, Seminars in Oncology Nursing. La Mesa, 2006: Vol. 22, Issue 3, p185-193.

Respiratory Tract Infections

DEFINITION

- **Respiratory tract infections** (RTIs) include infections of the sinuses, throat, airways, or lungs.
- **Upper RTIs** include acute rhinosinusitis and other nonspecific causes of respiratory symptoms not extending into the bronchi or alveoli.
  - » **Rhinosinusitis** is an inflammation or infection of the nasal or paranasal mucosa.
- **Lower RTIs** include bronchitis and pneumonia.
  - » **Bronchitis** is a self-limited inflammation of the large airways (bronchi).
  - » **Pneumonia** is an infection of the alveoli affecting one or both lungs.
- **Chronic obstructive pulmonary disease (COPD) exacerbation** is characterized by an acute inflammation of the airways with restricted airflow and reduced oxygenation.

ETIOLOGY AND RISK FACTORS

- Most bacterial RTIs are caused by commensal oropharyngeal flora, which migrate to the site of infection or, in pneumonia, are aspirated into the lungs.
- Viruses and some atypical bacteria are transmitted via airborne droplets.
- Rarely, pneumonia may also occur due to hematogenous spread from another infected body site (e.g. endocarditis, septic joint, or infected IV catheter).
- RTIs are typically monomicrobial infections; Table 1 lists the most common causative organisms.

TABLE 1 – RTI PATHOGENS

BACTERIAL	VIRAL
"Typical" respiratory bacteria	• Influenza • Rhinovirus (common cold) • Coronavirus • Respiratory syncytial virus (RSV) • Parainfluenza • Metapneumovirus • Adenovirus
• *Streptococcus pneumoniae* • *Haemophilus influenzae* • *Moraxella catarrhalis*	
"Atypical" respiratory bacteria	
• *Mycoplasma pneumoniae* • *Legionella pneumophila* • *Chlamydia pneumoniae*	
Staphylococcus aureus **(MSSA or MRSA)**	
Enterobacteriaceae if frequent healthcare exposures	
• *E. coli* • *Klebsiella* spp. • *Pseudomonas aeruginosa*	

- Bronchitis and almost all upper RTIs are caused predominantly by viruses.
  - » The typical respiratory bacteria may uncommonly cause rhinosinusitis (< 10% of cases).
- COPD exacerbations may be caused by viruses, bacteria, or non-infectious environmental irritants.
- Pneumonia may be caused by viruses or bacteria.
  - » *S. pneumoniae* is the most common bacterial cause of pneumonia.
  - » *M. pneumoniae*, *L. pneumophila*, and *C. pneumoniae* may cause pneumonia and are referred to as "atypical" respiratory pathogens due to the fact that they replicate within host immune cells.
    - ° *L. pneumophila* is a rare cause of pneumonia, often due to contaminated water.
  - » Influenza may be a cause of pneumonia during flu season.
- Risk factors for RTI include the following:

- Older age (> 65 years)
- Pre-existing respiratory disease (e.g. asthma, COPD)
- Smoking
- Comorbidities increasing aspiration risk (e.g. dysphagia due to stroke, neurologic disorders/ epilepsy, alcoholism, aging)
- Immunosuppression
- Malnutrition
- Regular contact with children
- Medications
  - Proton pump inhibitors (PPIs)
  - H2-blockers (less than PPIs)
  - Antipsychotics
  - Corticosteroids
  - Immunosuppressants
- Several factors increase the risk for aspiration pneumonia (**Table 2**)

TABLE 2 – RISK FACTORS FOR ASPIRATION PNEUMONIA

RISK FACTORS
• Dysphagia
• History of coughing following eating/drinking
• Decreased level of consciousness
• Mechanical disruption of glottic closure (e.g., intubation, tube feeding)
• Poor dental hygiene
• Advanced age

DIAGNOSIS

- Signs and symptoms (S/S) of rhinosinusitis may include nasal discharge, nasal congestion or obstruction, facial fullness or pressure, fever, headache, ear pain/pressure/fullness, halitosis, dental pain, cough, and fatigue.
  - Allergies, environmental exposures, and patients with facial anatomic abnormalities may present with similar symptoms.
- Patients with rhinosinusitis and the following clinical features may have an increased likelihood of bacterial infection:[1]
  - Persistent symptoms for more than 10 days
  - Onset of severe symptoms or signs of high fever (> 39°C)
  - Purulent nasal discharge or facial pain lasting for at least 3 consecutive days
  - "Double-sickening" (new onset of fever, headache, or increasing nasal discharge after 5-6 days of improving symptoms)
- The following signs and symptoms may be observed with lower RTI, particularly pneumonia (**Table 3**)

TABLE 3 – CLINICAL CHARACTERISTICS OF LOWER RTI

RESPIRATORY S/S	GENERAL INFECTION S/S	OTHER S/S
• Productive cough • Shortness of breath • Pleuritic chest pain • Poor O_2 saturation • Diminished breath sounds • Rales/rhonchi heard on lung auscultation	• Fever • Leukocytosis • Chills • Tachycardia • Hypotension • Clammy, blue skin	• Nausea/vomiting • Joint pain • Muscle aches/fatigue

- Patients with bronchitis typically will have initial nasal symptoms, then progress to a persistent productive or unproductive cough. This cough may last up to 6 weeks.
  - The presence of purulent sputum should not be taken as a definite indication that bacterial infection is present. Purulence indicates the presence of inflammatory cells or sloughed mucosal epithelial cells, which may also occur in response to viral infection or general inflammation.
  - Systemic signs of infection are typically absent or mild.
- "Pneumonia mimics", including congestive heart failure (CHF) and non-bacterial COPD exacerbations, may present with non-specific radiographic findings and respiratory symptoms (e.g. cough, sputum production, dyspnea, and tachypnea) that cannot be reliably differentiated from pneumonia.
- Radiography

- The presence of a new or worsening infiltrate/consolidation on chest x-ray is consistent with a diagnosis of pneumonia.
  - This represents the movement of immune cells and fluid into the lung in response to inflammation.
  - Pneumonia without radiographic findings is extremely rare in the absence of profound neutropenia or severe dehydration.
  - Radiography alone cannot distinguish between viral or bacterial pneumonia.
- For pneumonia, chest x-rays will often still show an infiltrate even after the infection is resolved. The typical time needed to clear on x-rays is 2-4 weeks for immunocompetent individuals and up to 8 weeks or more for patients who are immunocompromised.
- An infiltrate/consolidation may also represent (non-bacterial) exacerbations of CHF or COPD and thus in itself is not diagnostic of pneumonia.

- Cultures and laboratory tests
  - Blood cultures
    - Positive in 1-20% of pneumonia cases and when positive indicate the likely bacterial pathogen. However, use is not routinely indicated for hemodynamically stable patients in the outpatient setting.
    - Not indicated for other RTIs due to poor yield.
  - Sputum cultures
    - Reasonable to forgo due to the high activity of empiric antibiotic regimens against the common bacteria implicated in pneumonia.
      - If infection with a resistant organism is likely, a sputum culture may be considered.
    - Most patients (>75%) are unable to produce a quality sample, and attempts at collection may cause patient discomfort (more than one tablespoon of sample is needed).
      - Split/saliva is not an appropriate sample for culture as this represents only oral flora.
    - Of note, the growth of an organism on sputum culture could also represent respiratory tract colonization rather than infection.
      - Therefore, clinically improving patients should be continued on their original therapy even if a culture shows a resistant organism, as the resistant organism is likely a colonizer and not the cause of the patient's infection in this circumstance.
    - Interpretation of quality cultures
      - Positive culture indicates the likely bacterial pathogen for lower RTI.
      - Negative cultures may be used to rule out infection with Enterobacteriaceae, *P. aeruginosa*, or *S. aureus*.[2]
      - The atypical bacteria will not grow on sputum culture, and *S. pneumoniae* also grows poorly. Therefore, a negative culture cannot be used to state that the patient is not infected.
  - Rapid antigen tests for influenza can be used to confirm infection with influenza A or B.
    - These tests are specific but not 100% sensitive; it may be reasonable to initiate antiviral therapy for influenza even with a negative result if there is a strong clinical suspension for influenza based on local prevalence and clinical presentation.
  - Tests not typically conducted in the hospice setting
    - Pathogen-specific tests include MRSA nasal PCR, viral PCR, *M. pneumoniae* and *C. pneumoniae* serology, and urinary antigen tests for *L. pneumophila* and *S. pneumoniae*.
      - Generally, the costs and administration burdens of this testing will outweigh the benefits in the hospice setting.
    - Procalcitonin is an inflammatory biomarker that has demonstrated utility in distinguishing RTI caused by bacteria from viral or non-infectious causes. However, its use is predominantly limited to inpatient settings at this time.

CLINICAL INSIGHTS

ANTIMICROBIAL THERAPY

- Upper RTI
  - » Antibiotics should be avoided as these infections are virtually always viral and the patient is more likely to experience an acute antibiotic-related complication than prevent an infection-related complication.[3]
    - ° Approximately 1 in 4,000 chance that an antibiotic may prevent a serious complication.
    - ° Approximately 1 in 1,000 chance of requiring a visit to the emergency department because of an adverse reaction to the antibiotic
    - ° Up to 25% chance of causing antibiotic-associated diarrhea.
    - ° Reducing the use of unnecessary and inappropriate antibiotics for RTI supports antimicrobial stewardship by reducing the risk of drug resistance and may help promote patient comfort by avoiding preventable drug-drug interactions and antibiotic adverse effects, including *Clostridium difficile* associated diarrhea (CDAD).
  - » Rhinosinusitis
    - ° For nonbacterial rhinosinusitis, symptomatic management with nasal decongestants, saline irrigation, and/or mucolytics is recommended.
    - ° For patients with suspected bacterial rhinosinusitis, nasal decongestants and antihistamines are not recommended, as they have not been associated with symptomatic improvement when bacterial infection was present, and may induce rebound congestion and inflammation. Intranasal saline irrigation or intranasal corticosteroids may still be used.[1]
    - ° Even with potential bacterial sinusitis, patients with non-severe symptoms may be reasonably observed without antibiotic treatment for 3 days to avoid unnecessary antibiotic use.
      - › When otherwise healthy outpatients were advised to use a watch and wait approach for a few days before filling their antibiotic prescription, approximately 70% had resolved symptoms without the need for antibiotic therapy.[4]
    - ° If indicated, antibiotic therapy should be directed toward the typical respiratory pathogens.
      - › Amoxicillin/clavulanate is first-line due to excellent activity and a more favorable adverse effect profile.
      - › Doxycycline may be used as second-line therapy.
      - › Levofloxacin or moxifloxacin should be restricted to patients unable to receive other agents in accordance with a 2016 FDA safety review advising against routine use of fluoroquinolones for this indication due to the potential for serious adverse effects and limited benefit.[5]
- Bronchitis
  - » Routine antibiotic treatment is not recommended for bronchitis due to the low likelihood of a bacterial pathogen, the self-limiting infection course, and risk for adverse events.
    - ° A Cochrane review of 17 randomized, controlled trials found limited evidence to support the use of antibiotics for acute bronchitis, with no significant difference in clinical improvement over placebo and significantly more adverse events when antibiotics were used.[6]
    - ° A randomized trial comparing 10 days of amoxicillin/clavulanate, ibuprofen, and placebo for bronchitis showed no significant differences among the groups in the number of days to cough resolution, with adverse events more common in the antibiotic group.[7]
  - » Inhaled bronchodilators may be beneficial for patients with wheezing and underlying pulmonary disease (e.g. asthma, COPD), but they are not recommended for cough reduction in patients without pulmonary comorbidities due to no statistical benefit and risk for adverse effects of tremor, shaking, or nervousness (number needed to harm = 2).[8]
  - » Although not shown to shorten bronchitis duration, use of cough suppressants (dextromethorphan or codeine), expectorants (guaifenesin), first-generation antihistamines (diphenhydramine), or decongestants (phenylephrine) may offer symptomatic relief to some patients, though this should be weighed against the potential for adverse effects.[9]

- » If antibiotic therapy is warranted, 5-7 days of amoxicillin/clavulanate, doxycycline, or azithromycin may be used.
  - › Fluoroquinolones should be restricted to those without alternative treatment options in accordance with the 2016 FDA safety review advising against front-line use of fluoroquinolones for this indication.[5]

- COPD exacerbation
  - » Short-acting bronchodilator therapy is recommended for acute treatment.[10]
  - » Corticosteroid therapy (e.g. prednisone 40mg daily for 5 days) is generally recommended to improve lung function and shorten recovery time.[10]
  - » The GOLD guidelines recommend antibiotic therapy for patients with COPD exacerbation and increased sputum purulence plus increased shortness of breath or increased sputum volume, predominantly based on data from critically ill inpatients.[10]
  - » Although the aforementioned GOLD guidelines recommend antibiotic treatment, benefit of therapy should not routinely be expected. Even among hospitalized patients, viruses are the most common organisms implicated in COPD exacerbations with an infectious etiology[13]; thus, for the majority of patients, antibiotics are not anticipated to provide any treatment benefit.
    - ° Exacerbations, even when bacteria are present, are often self-limiting without antibiotic therapy.[14]
    - ° Increased antibiotic prescribing is associated with increased resistance of *S. pneumoniae*, the most virulent organism implicated in COPD exacerbation.[15]
  - » Further, in the outpatient setting, antibiotics have not been shown to reduce mortality or short-term treatment non-response in patients receiving treatment for acute exacerbations.
    - ° Outpatients with mild-to-severe COPD receiving doxycycline + prednisone for acute exacerbations did not have reduced time to next exacerbation when compared to patients receiving prednisone with placebo.[11]
    - ° Thus, some experts recommend further restriction of antibiotics in the primary care setting to patients with no recovery after 4 days of therapy with corticosteroids and bronchodilation in association with fever and persistent FEV_1 < 30%.[12]
  - » Based on the questionable benefit of antibiotic therapy in non-hospitalized patients, and the potential for resistance and other adverse drug effects, withholding initial antibiotic therapy remains a reasonable option for outpatients receiving hospice care.
    - ° Amoxicillin/clavulanate, doxycycline, or azithromycin for 5-7 days are reasonable treatment options when antibiotic therapy is warranted.
    - ° Fluoroquinolone therapy should be restricted to patients unable to receive one of the above agents or with a history of *P. aeruginosa* respiratory infection.

- Pneumonia
  - » Although antibiotic therapy for pneumonia is generally recognized as appropriate given the increased likelihood of a bacterial pathogen relative to upper RTI and high associated morbidity and mortality, it may be reasonable under some circumstances to withhold antibiotic therapy based on the patient's goals of care (see Anticipated Treatment Benefit section).
  - » Both typical and atypical respiratory bacteria are implicated in pneumonia.
    - ° Any antibiotic regimen should have adequate activity against *S. pneumoniae*.
    - ° The atypical bacteria are intrinsically resistant to β-lactams and other cell-wall active agents. Active antibiotic classes are fluoroquinolones, macrolides, and tetracyclines.
  - » Guideline-recommended regimens for outpatient pneumonia treatment include an oral β-lactam plus doxycycline or a macrolide (for atypical activity) or monotherapy with a respiratory fluoroquinolone for 5-7 days.[16] (**Table 4**)
    - ° The respiratory fluoroquinolones are levofloxacin and moxifloxacin.

- Ciprofloxacin has greater efficacy than levofloxacin or moxifloxacin for the treatment of pneumonia caused by *P. aeruginosa*, but has poor activity against *S. pneumoniae* and thus is not recommended as empiric therapy (note: it is a common misconception that ciprofloxacin has "poor lung penetration", but the rationale against its use in this scenario is based on lack of activity).

TABLE 4 – GUIDELINE RECOMMENDED REGIMENS FOR OUTPATIENT TREATMENT OF PNEUMONIA

RECOMMENDED REGIMENS		
β-lactam [a b]	*-Plus-*	Doxycycline [c] -or- Macrolide [c]
-or-		
Respiratory fluoroquinolone (levofloxacin or moxifloxacin)		

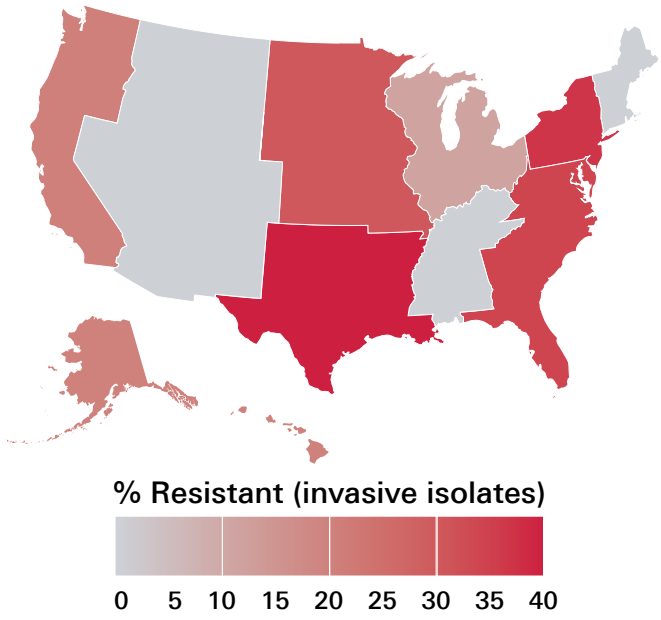
a – amoxicillin-clavulanic acid or 2nd/3rd generation cephalosporin preferred

b – for *S. pneumoniae* coverage

c – for atypical coverage

- Selection of combination therapy with β-lactam plus doxycycline or a macrolide versus monotherapy with a respiratory fluoroquinolone should be based on patient-specific factors (e.g. risk factors for drug-resistant *S. pneumoniae* (**Table 5**), potential drug-drug interactions) and local resistance patterns.
  - Levofloxacin may be preferred for patients with a history of pneumonia caused by *P. aeruginosa*.
- Approximately 25% of *H. influenzae* and 95% of *M. catarrhalis* produce a β-lactamase; thus, penicillin/β-lactamase inhibitor combinations (e.g. amoxicillin/clavulanate) or 2nd/3rd generation cephalosporins should be used.
- Patients without risk factors for drug-resistant *S. pneumoniae* (**Table 5**) may also be considered for doxycycline or macrolide monotherapy. Note that most hospice patients will have at least one risk factor.
  - Doxycycline monotherapy is typically preferred over macrolide monotherapy due to increasingly high rates of *S. pneumoniae* macrolide resistance, particularly in geographical areas know to have higher than typical resistance (**Figure 1**).[17]
  - Additionally, doxycycline is associated with over 4-fold reduced risk for development of *C. difficile* infection.[18]

FIGURE 1 – RESISTANCE MAP OF *S. PNEUMONIAE* TO MACROLIDE ANTIBIOTICS



Source: Center for Disease Dynamics, Economics & Policy (cddep.org); accessed online June 2019 at: https://resistancemap.cddep.org/CountryPageSub.php?country=United+States

- As an alternative to the guideline-recommended regimens, some experts suggest that β-lactam monotherapy should be preferred empirically for elderly patients due to a potentially lower likelihood for atypical bacteria and the more favorable adverse event profile of the β-lactams compared to other antibiotic classes.[19]
- Oral linezolid may be considered for empiric or definitive treatment of MRSA pneumonia.

- Because of its high cost, empiric use in hospice is rare and it should only be considered for high-risk patients (e.g. prior history of MRSA pneumonia) and given in addition to the typical pneumonia antibiotics.

TABLE 5 – RISK FACTORS FOR DRUG-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

RISK FACTORS
• Antibiotic therapy in past 3 months
• Chronic heart, lung, liver, or renal disease
• Diabetes
• Alcoholism
• Malignancy
• Asplenia
• Immunocompromise

» Aspiration pneumonia[28]

- In addition to the bacteria spp. that broadly cause pneumonia, a distinguishing feature of aspiration pneumonia is that anaerobes may also be implicated.
  - Modern studies of both outpatient and inpatient elderly populations show anaerobes represent less than 20% of organisms in aspiration.[29–30]
  - Oral anaerobes are generally susceptible to β-lactams, even those without a beta-lactamase inhibitor (e.g., penicillins, cephalosporins).
  - Therefore, the general pneumonia treatment strategy above is usually sufficient in treating most aspiration pneumoniae.
- If an anaerobic bacterial cause is strongly suspected (e.g., patients with poor dental hygiene or foul smelling sputum), the drug regimen could be expanded to provide greater anaerobic coverage.
  - Among the treatment options for pneumonia listed above, amoxicillin-clavulanic acid and moxifloxacin are inherently good choices because of anaerobic coverage and adequate empiric coverage against bacteria spp. that are generally implicated in pneumonia. There is some coverage with doxycycline, but levofloxacin and macrolides do not provide anaerobic coverage.
  - For regimens without amoxicillin-clavulanic acid or moxifloxacin, metronidazole or clindamycin could be added, but neither should be used as monotherapy.
- As with non-aspiration pneumonia, duration of treatment is typically 7 days.
- Prophylactic antibiotic therapy following an aspiration event is not beneficial.[31]

» Influenza pneumonia

- Antiviral therapy may be considered for patients with influenza at high risk for complications, including:[20]
  - Severe, complicated, or progressive illness
  - Age > 65 years
  - Chronic heart, lung, liver, renal, or hematologic disease
  - Immunosuppression
- Oseltamivir is the best studied antiviral and is generally well-tolerated, with good influenza activity.
  - "High-dose" oseltamivir (150mg PO BID) has not been shown to be beneficial and may increase the risk for gastrointestinal adverse effects.
- Zanamivir is only available as an inhalation device that requires patients capable of drawing a deep, steady breath.
  - Not well-studied in patients with underlying respiratory disease and may cause bronchospasm

ANTICIPATED TREATMENT BENEFIT

- Antibiotic therapy is not anticipated to provide benefit for the majority of patients with upper RTI or bronchitis due to their predominantly viral etiology and low likelihood for disease progression.

- » In a meta-analysis of antibiotics versus placebo for upper RTI, antibiotics were no better than placebo at improving RTI symptoms and were associated with a nearly 3-fold increased risk of adverse effects.[21]

- The use of antibiotics for pneumonia, although generally regarded as appropriate, is controversial within the hospice setting due to differing effects on mortality and patient comfort.
  - » In an analysis of over 300 patients with advanced dementia, antibiotic therapy for pneumonia was associated with increased survival 90 days after the pneumonia episode (~60% survival versus 33% survival).[22]
    - ° Oral antibiotic therapy was as effective at prolonging life as parenteral agents.
    - ° However, among the patients who did not die, lower comfort levels were observed among the patients who received antibiotic treatment, with greater discomfort when more aggressive treatments (e.g. IV antibiotics) were used.[22]
  - » Thus, goal-directed care is recommended and withholding of antibiotics for pneumonia may be preferred for patients whose primary goal of care is comfort.
    - ° Alternative palliative measures include antipyretics, opioids for dyspnea and pain, anxiolytics, anticholinergics to reduce mucous, and hydration.

- When antibiotic therapy is used for pneumonia, some improvement or response is typically observed within 72 hours.
  - » Longer antibiotic courses (> 7 days) are no better if early clinical response and increase the risk for future drug resistance.
  - » Hospice patients may potentially have a lower likelihood of symptomatic improvement with antibiotic therapy. In one study of over 200 hospice cancer patients with nonspecific RTI, less than half of patients had symptomatic improvement, which is consistent with other smaller studies in this population.[23] However, these results may also be attributed to non-bacterial causes of respiratory symptoms.

PREVENTION AND SUPPRESSIVE THERAPY

- Antibiotic prophylaxis is rarely indicated for RTI.
  - » Upper RTIs are seldom caused by bacteria.
  - » As most bacterial RTIs are caused by commensal oropharyngeal flora, antibiotic prophylaxis does not prevent bacterial acquisition or eradicate the causative pathogens.
  - » Increased antibiotic exposures promote *S. pneumoniae* resistance.[15]

- Some evidence suggests a modest benefit of azithromycin suppressive therapy for reducing the number of COPD exacerbations in patients with multiple recurrences.[24]
  - » The potential for reduced exacerbations should be weighed against the risk for hearing loss, tinnitus, QTc prolongation, and drug resistance.

- Prophylaxis against influenza with oseltamivir may be considered for individuals at high risk for complications from influenza, or in the case of an institutional outbreak.[20]
  - » Vaccination provides superior protection and should be the preferred means of prophylaxis unless it is contraindicated or would cause significant patient discomfort.

- Current evidence does not support routine use of natural products for RTI prevention or treatment (e.g. zinc, *Echinacea*, vitamin C). Use may be considered for patients previously finding benefit with such therapies.
  - » Zinc may reduce the duration of cold symptoms by up to 1 day without affecting symptom severity, though the data are inconsistent.[25]
    - ° However, the use of oral zinc is also associated with a bad taste and nausea, while intranasal zinc has been linked to a loss of smell.
  - » Prophylactic use of *Echinacea* products was associated with a small reduction in colds (number need to treat to prevent one cold = 8), but also a higher rate of adverse effects, predominantly gastrointestinal or dermatologic in nature.[26]
  - » In a meta-analysis of over 10,000 patients, vitamin C supplementation did not reduce the incidence of colds or meaningfully impact symptom duration.[27]

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
β-LACTAM ANTIBIOTICS [16, 32, 33]				
Amoxicillin/ clavulanate (Augmentin)	Pneumonia (ER Tablet): 2g PO Q12H X 5-7 days Other RTI: 500mg PO Q8H or 875mg PO Q12H X 5-7 days	ER Tablet*: 1,000/62.5mg Oral Suspension: 125/31.25mg/5ml, 200/28.5mg/5ml, 250/62.5mg/5ml, 400/57mg/5ml, 600/42.9mg/5ml Tablet: 250/125mg, 500/125mg, 875/125mg Tablet Chewable: 200/28.5mg	• First-line option for RTI when antibiotic therapy is indicated (in addition to doxycycline or a macrolide when used for pneumonia) • Increased incidence of diarrhea (take with food) • Requires renal adjustments • The ratios of amoxicillin to clavulanate vary among formulations (e.g., 4:1, 7:1, 14:1). Products with different ratios are not always therapeutically interchangeable.	Y/N*
Cefpodoxime (Vantin)	200mg PO Q12H X 5-7 days	Oral Suspension: 50mg/5ml, 100mg/5ml Tablet: 100mg, 200mg	• Other oral cephalosporins may be substituted depending on available formulary agents and pathogen susceptibility. However, 1st generation cephalosporins (eg, cephalexin) should be avoided due to potential *H. influenzae* and *M. catarrhalis* resistance. • Requires renal adjustments	Y
Cefuroxime (Ceftin)	500mg PO Q12H X 5-7 days	Oral Suspension: 125mg/5ml Tablet: 250mg, 500mg		N (strong bitter taste)
MACROLIDE ANTIBIOTICS [16, 32, 33]				
Azithromycin (Zithromax)	RTI: 500mg PO once on Day 1, then 250mg Q24H on Days 2 to 5 RTI Max dose: 500mg PO Q24H X 5 days Suppression of COPD exacerbation: 250mg PO Q24H	Oral Suspension: 100mg/5ml, 200mg/5ml Tablet: 250mg, 500mg, 600mg	**Clarithromycin** • May inhibit CYP3A4 and azithromycin may inhibit CYP1A2 • ER tablet should be taken with food. • Requires renal adjustments if CrCl < 30ml/min **Macrolides** • Adverse drug effects of taste perversion, QTc prolongation, hearing loss (prolonged use), tinnitus, hepatotoxicity (rare) • Substitution of erythromycin not recommended due to reduced efficacy, increased drug interactions and GI side effects, and cost	Y
Clarithromycin (Biaxin)	IR: 250-500mg PO Q12H X 5-7 days ER: 1,000mg PO Q24H X 5-7 days	Oral Suspension: 125mg/5ml, 250mg/5ml Tablet: 250mg, 500mg Tablet (ER)*: 500mg		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
TETRACYCLINE ANTIBIOTICS [16, 32, 33]				
Doxycycline (Vibramycin)	Pneumonia: 100mg PO Q12H X 5-7 days COPD exacerbation: 200mg PO Q24H X 5-7 days	Capsule:100mg Oral Suspension: 25mg/5ml Tablet: 100mg	• Administer with meals to minimize GI discomfort • Have patient take with a glass of water and sit upright for at least 30 minutes after administration to reduce risk of esophageal irritation • Use with caution in those with dysphagia • May cause photosensitivity (sunscreen with UVA protection recommended) • Separate antacids and calcium/iron supplements by 2 hours on either side of use • Doxycycline monohydrate formulation may have improved GI tolerability due to reduced acidity, though absorption may be reduced for patients receiving acid suppression	Y
FLUOROQUINOLONE ANTIBIOTICS [32, 33]				
Levofloxacin (Levaquin)	Pneumonia: 750mg PO Q24H X 5-7 days Other RTI: 500mg PO Q24H X 5-7 days	Oral Solution: 25mg/ml Tablet: 250mg, 500mg, 750mg	**Fluoroquinolones** • Not recommended for upper RTI if other agents can be used (FDA safety review) • Multiple potential ADEs, most commonly altered mental status/delirium. Others include photosensitivity, QTc interval prolongation, tendon rupture (rare), and aortic dissection (rare). • Separate antacids and calcium/iron supplements by several hours on either side of dose as directed by product labeling • May increase INR in patients receiving warfarin • Ciprofloxacin is not considered a respiratory fluoroquinolone, due to poor activity against *S. pneumoniae*, and should not be used unless confirmed susceptibility **Levofloxacin** • Levofloxacin has better activity against *P. aeruginosa* than moxifloxacin • Levofloxacin requires renal adjustments	Y
Moxifloxacin (Avelox)	400mg PO Q24H X 5-7 days	Tablet: 400mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MISCELLANEOUS ANTIBIOTICS [16, 28, 32]				
Clindamycin (Cleocin)	450mg PO TID x 7 days	Capsule: 75mg, 150mg, 300mg Oral Solution: 75mg/5ml	• May be used for treatment of aspiration pneumonia when anaerobic cause is suspected and when patient has PCN allergy precluding use of amoxicillin-clavulanate • Increased risk of *Clostridium difficile* infection • Solution has very poor taste leading many patients to refuse administration	Y
Linezolid (Zyvox)	600mg PO Q12H X 5-7 days	Oral Suspension: 100mg/5ml Tablet: 600mg	• May be used if empiric or definitive treatment of MRSA pneumonia is needed. • Increased risk for neuropathies, thrombocytopenia, GI bleeding with long term use (>2 weeks) • Expensive	Y
Metronidazole (Flagyl)	500mg PO TID x 7 days	Tablet: 250mg, 500mg	• May be used for treatment of aspiration pneumonia in conjunction with other agents if anaerobic cause suspected, but should not be used as monotherapy • Administer with food • May cause metallic taste • Avoid alcohol during therapy and for 24-72 hours after last dose (may cause severe vomiting) • Reduce dose if severe liver disease	Y
ANTIVIRAL AGENTS [20, 32]				
Oseltamivir (Tamiflu)	Influenza (treatment): 75mg PO Q12H X 5 days Influenza (prophylaxis): 75mg PO Q24H	Capsule: 30mg, 45mg, 75mg Oral Suspension: 6mg/ml	• Potential nausea/vomiting, skin reactions, neuropsychiatric effects (rare, increased risk if Japanese ancestry) • Requires renal adjustments • Post-exposure prophylaxis should be continued for 1 week after last exposure, or, with an institutional outbreak, for at least 2 weeks total and 1 week after the onset of symptoms in the last case identified. • Pre-exposure prophylaxis is only indicated for unvaccinated individuals. It should be continued for 2 weeks (if given in conjunction with vaccination) or for the duration of influenza activity.	Y

References

1. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54:e72-e112.
2. Zilberberg MD, Shorr AF. Healthcare-associated pneumonia: the state of evidence to date. Curr Opin Pulm Med. 2011;17:142-7.
3. Linder JA. Editorial commentary: antibiotics for treatment of acute respiratory tract infections: decreasing benefit, increasing risk, and the irrelevance of antimicrobial resistance. Clin Infect Dis. 2008;47:744-6.
4. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotic prescriptions for respiratory infections. Cochrane Database Syst Rev. 2017;9:CD004417.
5. FDA Drug Safety Communication. FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. US Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/ucm500143.htm. Accessed May 3, 2019.
6. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. Cochrane Database Syst Rev. 2017;6:CD000245.
7. Llor C, Moragas A, Bayona C, Morros R, Pera H, Plana-Ripoll O, et al. Efficacy of anti-inflammatory or antibiotic treatment in patients with non-complicated acute bronchitis and discoloured sputum: randomised placebo controlled trial. BMJ. 2013;347:f5762.
8. Becker LA, Hom J, Villasis-Keever M, van der Wouden JC. Beta2-agonists for acute cough or a clinical diagnosis of acute bronchitis. Cochrane Database Syst Rev. 2015;(9):CD001726.
9. Chang CC, Cheng AC, Chang AB. Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. Cochrane Database Syst Rev. 2014;(3):CD006088.
10. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: 2019 report. www.goldcopd.org. Accessed May 3, 2019.
11. van Velzen P, Ter Riet G, Bresser P, Baars JJ, van den Berg BTJ, van den Berg JWK, et al. Doxycycline for outpatient-treated acute exacerbations of COPD: a randomised double-blind placebo-controlled trial. Lancet Respir Med. 2017;5:492-9.
12. Bathoorn E, Groenhof F, Hendrix R, van der Molen T, Sinha B, Kerstjens HA, et al. Real-life data on antibiotic prescription and sputum culture diagnostics in acute exacerbations of COPD in primary care. Int J Chron Obstruct Pulmon Dis. 2017;12:285-90.
13. Lieberman D, Lieberman D, Ben-Yaakov M, Lazarovich Z, Hoffman S, Ohana B, et al. Infectious etiologies in acute exacerbation of COPD. Diagn Microbiol Infect Dis. 200;40:95-102.
14. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 1987;106:196-204.
15. Hicks LA, Chien YW, Taylor TH Jr, Haber M, Klugman KP. Outpatient antibiotic prescribing and nonsusceptible Streptococcus pneumoniae in the United States, 1996-2003. Clin Infect Dis. 2011;53:631-9.
16. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2:S27-72.
17. Center for Disease Dynamics, Economics, and Policy. ResistanceMap. Available at https://resistancemap.cddep.org. Accessed May 5, 2019.
18. Doernberg SB, Winston LG, Deck DH, Chambers HF. Does doxycycline protect against development of Clostridium difficile infection? Clin Infect Dis. 2012;55:615-20.
19. van Heijl I, Schweitzer VA, Zhang L, van der Linden PD, van Werkhoven CH, Postma DF. Inappropriate use of antimicrobials for lower respiratory tract infections in elderly patients: patient- and community-related implications and possible interventions. Drugs Aging. 2018;35:389-98.
20. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. Clin Infect Dis. 2019;68:e1-e47.
21. Arroll B, Kenealy T, Falloon K. Are antibiotics indicated as an initial treatment for patients with acute upper respiratory tract infections? A review. N Z Med J. 2008;121:64-70.
22. Givens JL, Jones RN, Shaffer ML, Kiely DK, Mitchell SL. Survival and comfort after treatment of pneumonia in advanced dementia. Arch Intern Med. 2010;170:1102-7.
23. Reinbolt RE, Shenk AM, White PH, and Navari RM. Symptomatic treatment of infections in patients with advanced cancer receiving hospice care. J Pain Symptom Manage. 2005;30:175-82
24. Wenzel RP, Fowler AA 3rd, Edmond MB. Antibiotic prevention of acute exacerbations of COPD. N Engl J Med. 2012;367:340-7.
25. Singh M, Das RR. Zinc for the common cold. Cochrane Database Syst Rev. 2013;(6):CD001364.
26. Karsch-Völk M1, Barrett B, Kiefer D, Bauer R, Ardjomand-Woelkart K, et al. Echinacea for preventing and treating the common cold. Cochrane Database Syst Rev. 2014;(2):CD000530.
27. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev. 2013;(1):CD000980.
28. Bartlett, JG et al. Aspiration pneumonia in adults, Walters Kluwer – UpToDate, accessed online June 2019.
29. El-Solh, AA et al. Microbiology of severe aspiration pneumonia in institutionalized elderly, Am J Respir Crit Care Med, 2003; 167(12): 1650-4.
30. Tokuyasu, H. et al. Effectiveness of meropenem for the treatment of aspiration pneumonia in elderly patients, Intern Med, 2009; 48(3): 129-35.
31. Dragan, V. et al. Prophylactic antimicrobial therapy for acute aspiration pneumonitis, Clin Infect Dis, 2018; 67(4): 513-18.
32. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020.
33. Metlay, Joshua et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. American Thoracic Society and Infectious Diseases Society of America. American Journal of Respiratory and Critical Care Medicine, Volume 200, Issue 7, 1 October 2019, Pages e45-e67

Skin & Soft Tissue Infections - Bacterial

DEFINITION

- **Skin and soft tissue infections (SSTIs)** refer to a collection of clinical infectious syndromes involving layers of skin and underlying soft tissues, but excluding muscle or bone.
- **Recurrent SSTI** is usually defined as ≥ 2 SSTIs over a 6 month period at different body sites.
- **Purulent** refers to infections containing or discharging pus.
- Example SSTIs and their associated organisms include the following (**Table 1**):

TABLE 1 – UNCOMPLICATED SSTIS AND IMPLICATED BACTERIA

	SSTI	DESCRIPTION	COMMON ORGANISMS
Nonpurulent	Impetigo	Reddish superficial papules, vesicles, and pustules which form characteristic yellow crusts when ruptured	*Streptococcus* spp., *Staphylococcus* spp. (MSSA > MRSA)
	Ecthyma	Similar to impetigo but extending into the dermis; red, crusted ulcerated lesions	
	Cellulitis	Localized swelling and redness of the skin representing inflammation extending into the dermis	*Streptococcus* spp., *Staphylococcus* spp.
	Erysipelas	Similar to cellulitis but more superficial and with a raised, clearly demarcated border	
Purulent	Furuncle (boil)	Infection of a hair follicle extending into the subcutaneous tissue	*Staphylococcus* spp., *Streptococcus* spp.
	Carbuncle	Infection of multiple adjacent hair follicles; deeper penetration than furuncle	
	Abscess	Collection of pus within the dermis and deeper layers of the skin	
Polymicrobial	Diabetic foot infection	Lower extremity SSTI among diabetic individuals, excluding superficial (non-ulcerated) SSTI	*Staphylococcus* spp., *Streptococcus* spp., Enterobacteriaceae, anaerobes

ETIOLOGY AND RISK FACTORS

- Although most SSTIs are not cultured in clinical practice, based on clinical trial data it is generally accepted that most cases of cellulitis are caused by *Streptococcus* spp., particularly *Streptococcus pyogenes* (Group A Strep), as well as *Staphylococcus aureus*. This has also been observed when specifically looking at the hospice population.[1]
  - » These organisms naturally colonize the skin, but may establish infection following compromise of the protective skin barrier.
  - » Localized purulent infections such as skin abscess are most commonly caused by *S. aureus*, including methicillin-resistant strains (MRSA), though streptococci may be isolated from abscesses as well.
    - ° Factors associated with an increased risk for MRSA are listed in Table 2.
  - » Gram-negative bacteria and anaerobes do not play a major role in SSTIs, with the exception of complicated infections such as deeply ulcerated wounds (eg, some diabetic foot infections), bite wounds, and select cases of SSTI associated with trauma.

  - » *Enterococcus* spp. are occasionally isolated from skin, but are usually reflective of colonization rather than infection.
  - » *Pseudomonas aeruginosa* can cause clinical SSTI in individuals with significant immune compromise, but otherwise is rarely implicated.
- Risk factors for SSTI generally involve breaches of the skin barrier or conditions associated with impaired wound healing (**Table 2**):

TABLE 2 – RISK FACTORS FOR SSTI AND MRSA

SSTI RISK FACTORS	MRSA RISK FACTORS
• MRSA colonization (see right) • Skin breakdown (eg, trauma, bug bites, scratches, pre-existing skin disease) • Drug injections • Obesity • Immunocompromise • Poor hygiene • Venous insufficiency • Tobacco use • Prior SSTI • SGLT-2 inhibitors (eg, canagliflozin, dapagliflozin, empagliflozin)	• Prior MRSA infection/ known colonization • Frequent hospitalization • Homelessness, including residence in homeless shelters • Drug injections • Military recruits • Incarcerated individuals • Sharing items in contact with skin of colonized person (towels, razors, etc.) • Tattoos and piercings • Hemodialysis

DIAGNOSIS

- There is no laboratory test or biomarker specific for SSTI, so diagnosis is made based on patient signs and symptoms.
- Most SSTIs are localized to a single extremity (arm or leg).
- The four classic signs and symptoms associated with SSTI (cellulitis in particular) are:
  - » Spreading erythema (redness)
  - » Swelling (edema)
  - » Localized pain/tenderness
  - » Warmth around the infection site
- Swelling of regional lymph nodes may also be present.
- Patients with abscesses will have one or more fluctuant, tender, and painful nodules and may or may not have surrounding cellulitis. Purulent discharge may be observed and is often odorous.
- Systemic manifestations of infection (eg, fever, tachycardia, confusion, leukocytosis, and hypotension) are usually mild or absent, though rarely patients may be septic.
- Pain out of proportion to the wound and the apparent physical findings should raise suspicion for joint or bone injuries and prompt further clinical evaluation.
- Hospice patients may have skin wounds not reflective of bacterial infection (eg, due to injury, immobility, incontinence, bruising). Antibiotic therapy is not indicated in the absence of local or systemic signs and symptoms of infection.
  - » Additionally, comorbid illnesses such as peripheral vascular disease, venous stasis, and pressure ulcers contribute to non-infectious chronic skin changes.
- Noninfectious conditions that can mimic the symptoms of lower extremity cellulitis (eg, erythema, swelling, pain), grouped together under the category of "pseudocellulitis":
  - » Venous stasis or contact dermatitis
  - » Congestive heart failure (CHF)-associated edema
  - » Deep vein thrombosis (DVT)
  - » Gout
  - » Hematoma
- Pseudocellulilitis represents over 30% of all cellulitis diagnoses, and is a common cause of inappropriate antibiotic therapy.[2]
  - » In particular, bilateral cellulitis is extremely rare and almost always representative of CHF edema or stasis dermatitis.
  - » Edema-causing conditions should be ruled out before assigning a cellulitis diagnosis, especially for patients without systemic signs of infection.
- Less commonly, viral pathogens may be implicated in SSTI.
  - » Vesicular rashes, particularly located on the face, trunk, or genitals, may be reflective of herpes virus reactivation (eg, herpes simplex virus or varicella zoster), particularly in immunocompromised individuals.

- Cultures
  - » Fluid from incised and drained abscesses may be cultured if definitive pathogen identification and susceptibility testing is desired (eg, patient with multiple recurrences).
    - ° Not routinely indicated for nonseptic patients, as empiric antibiotic regimens generally have good activity against likely pathogens.
  - » Superficial skin swabs should not be sent for culture, as this is likely to represent commensal skin flora and not necessarily the organism(s) causing the infection.
  - » Blood cultures are not indicated in the absence of sepsis or severe immune compromise, as they have low yield (<5%) in SSTI.[3]
- Imaging
  - » Not routinely recommended
  - » May rule out causes of pseudocellulitis (eg, ultrasound to rule out DVT)
  - » May be considered for patients not responding to therapy to assess for complications (eg, x-ray to determine if foreign body present, CT/MRI to evaluate for osteomyelitis)

CLINICAL INSIGHTS

ANTICIPATED THERAPY BENEFIT

- SSTI-associated mortality is low for infections not causing hemodynamic instability, so the purpose of antimicrobial therapy for SSTI is to promote more rapid resolution of signs and symptoms.
- The potential risks and benefits of therapy, including the likelihood of SSTI diagnosis, should be carefully considered before initiating antibiotic treatment. For some patients, withholding antibiotic therapy may be the preferred option.
- Expected responses to antibiotic therapy:
  - » Initially (≤ 24-48 hours), cellulitis may appear to worsen despite active antimicrobial treatment. This is common and may be due to bacterial lysis or toxin release, which temporarily increases inflammation.
  - » A modest 20% reduction in redness and/or swelling at 48-72 hours is highly predictive of success at end of treatment.[4]
  - » Even with nonresponse at day 3, most infections will resolve with continued treatment, so it is recommended not to broaden antibiotic therapy in the first few days unless the infection appears to be rapidly progressing.[5]
  - » Of note, some residual redness and inflammation is expected at the completion of antibiotic therapy despite bacterial eradication, and will continue to slowly resolve without the need for additional antibiotics.
  - » Response to antibiotic therapy may be attenuated in the hospice population. In two studies of hospice patients with SSTI the rate of symptomatic improvement was low (≤ 50%) with antibiotic therapy despite high sensitivity to the agents used.[6, 7]

GENERAL CONSIDERATIONS

- Antimicrobial treatment of SSTI is directed toward selecting regimens with activity against streptococci and staphylococci.
- With respect to selecting empiric therapy, IDSA guidelines do not advocate for a single antibiotic agent over another due to a lack of superiority data.[8] Instead, a variety of antibiotic options may be considered depending on the likely bacterial etiology and patient-specific factors.
- The decision of whether or not to administer antibiotics active against MRSA is dependent upon clinical presentation (eg, relative likelihood of MRSA versus other pathogens for that specific SSTI), local epidemiology, and patient-specific risk factors [Table 2].
  - » Patients at low risk for MRSA should not receive MRSA-targeted regimens (unless needed due to allergy/intolerance to non-MRSA regimens).
    - ° Multiple modern randomized trials failed to show higher rates of clinical resolution of nonpurulent SSTI when a MRSA-active antibiotic is given with cephalexin therapy compared to cephalexin therapy alone.[9, 10]
    - ° TMP/SMX and clindamycin, the most commonly prescribed oral antibiotics for MRSA, have the highest rates of adverse effects leading to ED admission per prescription.[11]
  - » When MRSA is not suspected, cephalexin is potentially more effective than

trimethoprim-sulfamethoxazole (TMP/SMX) for SSTI treatment in hospice patients.[6, 7]
  - » For patients with MRSA risk factors, "dual coverage" for SSTI (cephalexin added to TMP-SMX) is not recommended given clinical data demonstrating the adequacy of TMP/SMX monotherapy.[12]

- Macrolide therapy is generally not recommended for SSTI due to growing *Streptococcus* spp. resistance.
- Unless there is involvement of prosthetic material, addition of rifampin as an adjunctive anti-MRSA agent for SSTIs is not recommended due to poor evidence supporting clinical benefit as well as its numerous significant drug-drug interactions and unpleasant adverse effect profile, including hepatotoxicity and orange discoloration of body fluids.[13]
- For patients with true (IgE-mediated) penicillin allergy, the safety of cephalosporin therapy is dependent on whether the specific cephalosporin is structurally similar to penicillin or amoxicillin.[14]
  - » Cephalexin and cefaclor have a 5% chance of cross-reactivity and should not be given to patients with a history of severe penicillin allergy (eg, angioedema, anaphylaxis) unless taken safely in the past.
    - ° Use in patients with documented minor reactions to penicillin (eg, rash) may be considered with careful monitoring.
  - » Cefuroxime and cefpodoxime are not structurally similar to penicillin or amoxicillin and may be administered with penicillin allergy.
- Drug interactions
  - » TMP/SMX
    - ° May interact with warfarin to increase bleeding risk through multiple mechanisms, though closer INR monitoring should be considered when starting any antimicrobial agent.
    - ° Patients receiving ACE-inhibitors or angiotensin receptor blockers (ARBs) are at increased risk of sudden death due to the combined hyperkalemic effects of both drugs. Risk is elevated in elderly patients, those with renal impairment, high dose TMP/SMX, or concomitant use of potassium-increasing medication.[15]
  - » Tetracycline antibiotics (eg, doxycycline, minocycline) are susceptible to inactivation and treatment failure when co-administered with metal cations like calcium, aluminum, magnesium, and iron, which are found in significant concentrations in certain foods (eg, dairy products, nutritional supplements), medications (eg, aluminum-magnesium hydroxide, magnesium hydroxide), and over-the-counter (OTC) supplements (eg, calcium, iron, magnesium).
    - ° Administer at least 2 hours before or after these products or foods.
  - » Linezolid has been associated with serotonin syndrome in case reports, however the real-world incidence is extremely low. Although use is not recommended for patients taking MAO inhibitors, it is not necessary to withhold other antidepressants (eg, SSRIs) during linezolid therapy.
- Renal dosing considerations
  - » TMP/SMX is generally not recommended in patients with renal failure due to its risk for hyperkalemia and the potential for reduced efficacy in this population, but use may be considered in the absence of other effective treatment options.
    - ° Reducing the dose to single-strength tablets is recommended with CrCl 15-30 ml/min.
  - » β-lactams (with the exception of dicloxacillin) and acyclovir/valacyclovir also require adjustment (see: Symptom guide appendix "Antibiotic Selection with Renal Impairment").

INFECTION-SPECIFIC RECOMMENDATIONS

- Purulent SSTIs
  - » Incision & drainage (I&D) is the mainstay of therapy for abscesses.
    - ° Simple abscesses that can be adequately drained do not require antibiotics.[16, 17]
    - ° Antibiotic therapy has not been shown to prevent abscess recurrence.[17]
  - » Abscesses with any of the following characteristics are considered complicated and generally should be treated with antibiotics in addition to I&D:

- Multiple sites of involvement
- Systemic manifestations of infection (persistent fever ≥100.4°F, tachycardia, leukocytosis)
- Significant surrounding cellulitis
- Immunocompromise
- Abscess located in area difficult to drain (eg, face, genitals)

» Furuncles and carbuncles will often drain spontaneously. However, if drainage is inadequate, I&D may be required.
» Most furuncles may be adequately treated by the application of moist heat alone (see Adjunctive Therapies section).
» If antibiotic therapy is indicated, one of the following antibiotics may be used:

- Cephalexin (if low MRSA risk)
- TMP/SMX
- Doxycycline or minocycline
- Clindamycin
- Linezolid

- Impetigo
  » Topical therapy with mupirocin or retapamulin is effective when there are a limited number of lesions.
  » Apply topical agents gently to avoid further skin breakdown and infection spread.
  » With more extensive disease, oral β-lactams such as dicloxacillin or cephalexin should be used.
    - TMP/SMX, doxycycline, and clindamycin are MRSA-active alternatives, however most *S. aureus* isolates are methicillin-susceptible.
- Ecthyma
  » Topical antibiotics are not recommended.
  » Oral antibiotic options are the same as for impetigo (see above).
- Cellulitis/erysipelas
  » Therapy is directed against streptococci and *S. aureus*, +/- MRSA.
    - Cephalexin may be preferred due to good *Streptococcus* spp. and MSSA activity and low adverse effect risk.
    - MRSA-active alternatives are TMP/SMX, doxycycline or minocycline, clindamycin, or linezolid.
    - Treatment with penicillin is generally not recommended due to lack of *S. aureus* coverage.
  » 5 days of treatment has been shown to be as effective as 10 days.[18]
- Diabetic foot infection
  » Infections without ulcer or with superficial ulcer only are generally monomicrobial infections caused by gram-positive organisms and may be treated like cellulitis (see above).[19]
  » Deeper ulcerations are often polymicrobial, so oral antibiotics with expanded gram-negative and anaerobic activity may be preferred:
    - Amoxicillin/clavulanate
    - Third generation cephalosporin (eg, cefpodoxime) + metronidazole or clindamycin
    - Moxifloxacin
- Herpes virus reactivation
  » Herpes simplex virus: valacyclovir 1g PO daily X 5 days or acyclovir 400mg PO TID X 5 days
  » Herpes zoster: valacyclovir 1g PO TID until lesions crust over (~7-10 days)
    - Gabapentin may be considered to help relieve neuropathic pain symptoms.

ADJUNCTIVE THERAPIES

- Elevate the affected limb to reduce edema and associated pain.
- For cellulitis, mark the margins of erythema to better monitor for progression or improvement of the infection.
- Short-duration corticosteroid therapy (eg, prednisone 40mg daily for 7 days) may be considered for nondiabetic patients with significant inflammatory response.[8]
- Warm compresses may relieve symptoms associated with furuncles and encourage drainage of purulent material.
- Cover draining lesions with sterile dressings.
- Careful handwashing is recommended after contact with infected lesions.

PREVENTION AND SUPPRESSIVE THERAPIES

- SSTI prevention involves methods to promote good skin care and hygiene, such as regular skin cleansing with soap and water (paying particular attention to skin folds) and keeping dry skin hydrated using emollients.
- Local skin decolonization using alcohol wipes is recommended prior to the administration of injections.
- For patients with uninfected skin ulcers, local wound care, including gentle washings, wet-to-dry dressings, and application of topical antibacterial creams may help prevent infection.
  - » Compression dressings or boots may also reduce edema and promote wound healing for ulcerated limbs.
- For patients with recurrent SSTIs caused by MRSA:
  - » Environmental hygiene measures are recommended
    - ° De-contamination of doorknobs, counters, toilet seats
    - ° Launder sheets/clothing/towels at high temperatures and change regularly.
  - » Use of MRSA decolonization strategies may be considered after optimizing hygiene measures.[13]
    - ° Nasal mupirocin for 5 days effectively eliminates short-term *S. aureus* carriage, with longer-term eradication success rates of approximately 60%.[20]
    - ° In addition to nasal treatment, topical body decolonization regimens may be used, which include use of chlorhexidine solution for 5-14 days or dilute bleach baths (1/4 cup bleach per 1/4 tub [13 gallons] of bathwater, or 1 teaspoon per 1 gallon) for 15 minutes twice weekly for up to 3 months.
    - ° Oral antibiotics are generally not recommended for decolonization but may be considered with continued SSTI recurrence despite the above measures.
- Except in the context of wound care, topical antibiotics are not effective for SSTI prevention and promote colonization with more resistant bacteria.
- Oral antibiotic therapy for SSTI suppression is not generally recommended, but may be considered if SSTI recurrences are having a significant negative impact on quality of life. Generally, narrow-spectrum agents are preferred:
  - » Penicillin VK 500mg PO twice daily
  - » Amoxicillin 250-500mg PO twice daily
  - » Clindamycin 150-300mg PO daily
    - ° Less preferred due to *C. difficile* risk
  - » Erythromycin 250mg PO once or twice daily
    - ° May consider substituting azithromycin for improved GI tolerability
- For recurrent HSV, suppressive therapy with acyclovir 400mg PO BID or valacyclovir 1g daily may be considered.[21]

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
β-LACTAM ANTIBIOTICS[8, 14, 18, 22 – 24]				
Amoxicillin/ clavulanate (Augmentin)	SSTI: 875mg PO Q12H X 5-7 days Diabetic foot infection: 875mg PO Q12H X 5-14 days	Chewable Tablet: 200/28.5mg ER Tablet*: 1,000/62.5mg Oral Suspension: 125/31.25mg/5ml, 200/28.5mg/5ml, 250/62.5mg/5ml, 400/57mg/5ml, 600/42.9mg/5ml Tablet: 250/125mg, 500/125mg, 875/125mg	• First-line agent for polymicrobial SSTIs (eg, bite infections, diabetic foot) • Increased incidence of diarrhea (take with food) • Requires renal adjustments • The ratios of amoxicillin to clavulanate vary among formulations (eg, 4:1, 7:1, 14:1). Products with different ratios are not always therapeutically interchangeable.	Y/N*
Cefpodoxime (Vantin)	Diabetic foot infection: 200mg PO Q12H X 5-14 days	Tablet: 100mg, 200mg Oral Suspension: 50mg/5ml, 100mg/5ml	• Option for polymicrobial SSTI (in addition to metronidazole or clindamycin for anaerobic activity) with penicillin allergy • Requires renal adjustments	Y
Cefuroxime (Ceftin)	Diabetic foot infection: 500mg PO Q12H X 5-14 days	Tablet: 250mg, 500mg Oral Suspension: 125mg/5ml		N (strong bitter taste)
Cephalexin (Keflex)	500mg PO Q6H X 5-7 days	Tablet: 250mg, 500mg Capsule: 250mg, 500mg, 750mg Oral Suspension: 125mg/5ml, 250mg/5ml	• First-line agent for SSTI w/ low MRSA risk • Use caution with significant penicillin allergy (~5% cross-reactivity risk) unless previously tolerated • Requires renal adjustments	Y
Dicloxacillin (Dycill)	250-500mg PO Q6H X 5-7 days	Capsule: 250mg, 500mg	• Administer on an empty stomach, with at least 120 ml of water • Do not administer while lying down or immediately prior to going to bed	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
SULFA DRUGS [18, 22]				
Trimethoprim/ Sulfamethoxazole (Bactrim)	1-2 DS tablet PO Q12H X 5-7 days	Oral Suspension: 40/200mg/5ml Tablet: 80/400mg (SS), 160/800mg (DS)	• MRSA activity • ADRs include photosensitivity, hyperkalemia, and bone marrow suppression (dose-dependent) • Take with fluids to prevent urinary crystallization • May increase INR in patients receiving warfarin via multiple mechanisms • Do not use with sulfa allergy • Avoid in patients with significant renal insufficiency or renal dose adjust if use necessary	Y
TETRACYCLINE ANTIBIOTICS [8, 18, 22]				
Doxycycline (Vibramycin)	100mg PO Q12H X 5-7 days	Capsule: 100mg Oral Suspension: 25mg/5ml Tablet: 100mg Tablet (DR)*: 100mg *Numerous other strengths exist*	• MRSA activity • Administer with meals to minimize GI discomfort • Have patient sit upright for at least 30 minutes after administration to reduce risk of esophageal irritation • Use with caution in those with dysphagia • May cause photosensitivity (sunscreen with UVA protection recommended) • Separate antacids and calcium/iron supplements by 2 hours on either side of use • *Delayed-release capsule may be opened but not crushed • Doxycycline monohydrate formulation may have improved GI tolerability due to reduced acidity, though absorption may be reduced for patients receiving acid suppressing drugs	Y/N*
Minocycline (Minocin)	100mg PO Q12H X 5-7 days	Capsule: 100mg Tablet: 100mg *Numerous other strengths exist*	• MRSA activity • Rare CNS toxicities and blue/purple skin discoloration • Separate antacids and calcium/iron supplements by 2 hours on either side of use	Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
FLUOROQUINOLONE ANTIBIOTICS [18, 22, 23]				
Moxifloxacin (Avelox)	Diabetic foot infection: 400mg PO Q24H X 5-14 days	Tablet: 400mg	• Option for polymicrobial SSTI with penicillin allergy • Multiple potential ADEs, most commonly altered mental status/delirium. Others include photosensitivity, QTc prolongation, tendon rupture (rare), and aortic dissection (rare). • Separate antacids and calcium/iron supplements by several hours on either side of dose as directed by product labeling • May increase INR in patients receiving warfarin	Y
MISCELLANEOUS ANTIBIOTICS [8, 13, 22, 25]				
Clindamycin (Cleocin)	300-450mg PO Q8H X 5-7 days Diabetic foot infection: 300-450mg PO Q8H X 5-14 days	Capsule: 75mg, 150mg, 300mg Oral Solution: 75mg/5ml	• MRSA activity (some) • May use for polymicrobial SSTI to add additional anaerobic activity (in combination with an antibiotic with activity against gram-negative organisms) • Increased risk for *Clostridium difficile* infection • Administer with a full glass of water to minimize esophageal irritation • Solution has very poor taste leading many patients to refuse administration	Y
Linezolid (Zyvox)	600mg PO Q12H X 5-7 days	Oral Suspension: 100mg/5ml Tablet: 600mg	• MRSA, VRE activity • With long-term use (>2 weeks), increased risk for neuropathies, thrombocytopenia, GI bleeding • Expensive	Y
Metronidazole (Flagyl)	Diabetic foot infection: 500mg PO Q8-12H X 5-14 days	Capsule: 375mg Tablet: 250mg, 500mg	• Used when additional anaerobic activity needed (use in combination with an antibiotic with activity against gram-positive and gram-negative organisms) • May cause metallic taste • Avoid alcohol during therapy and for 24-72 hours after last dose (may cause severe vomiting)	N (poor taste)

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
TOPICAL ANTIBIOTICS [13, 22]				
Chlorhexidine gluconate topical (Hibiclens)	MRSA decolonization: apply minimum amount necessary to cover skin or wound area and wash gently X 5-14 days	Liquid/solution: 2%, 4%	• Rinse application area with water before and after application • May cause local hypersensitivity, dryness, and erythema	N/A
Mupirocin (Bactroban, Centany)	Impetigo: Apply to affected area Q8H X 5 days MRSA decolonization: Apply to both nostrils Q12H X 5 days	Cream: 2% Ointment: 2%	• Cream preparation generally better tolerated, though ointment may be used if dry or scaly lesions (better hydration) • Discontinue use if local irritation occurs	N/A
Retapamulin (Altabax)	Impetigo: Apply a thin layer to affected area Q12H X 5 days	Ointment: 1%	• Discontinue use if local irritation occurs • Expensive	N/A
ANTIVIRAL AGENTS [21, 22]				
Acyclovir (Zovirax)	HSV (recurrence): 400mg PO Q8H X 5 days -OR- 800mg PO Q12H X 5 days HSV (suppression): 400mg PO Q12H Shingles: 800mg PO 5 times daily X 7 days	Capsule: 200mg Oral Suspension: 200mg/5ml Tablet: 400mg, 800mg	• Take with glass of water to prevent urinary crystallization • Requires renal adjustments	Y
Valacyclovir (Valtrex)	HSV (recurrence): 1g PO Q24H X 5 days HSV (suppression): 500-1,000mg PO Q24H Shingles: 1g PO Q8H X 7 days	Tablet: 500mg, 1,000mg	• Prodrug of acyclovir (modified formulation increases bioavailability to allow for less frequent daily dosing) • Take with glass of water to prevent urinary crystallization • Requires renal adjustments	N (poor taste)

References

1. Pereira J, Watanabe S, Wolch G. A retrospective review of the frequency of infections and patterns of antibiotic utilization on a palliative care unit. J Pain Symptom Manage. 1998;16:374-81.
2. Weng QY, Raff AB, Cohen JM, Gunasekera N, Okhovat JP, Vedak P, et al. Costs and consequences associated with misdiagnosed lower extremity cellulitis. JAMA Dermatol. 2017;153:141-6.
3. Mills AM, Chen EH. Are blood cultures necessary in adults with cellulitis? Ann Emerg Med. 2005;45:548-9.
4. Talbot GH, Powers JH, Fleming TR, Siuciak JA, Bradley J, and Boucher H. Progress on developing endpoints for registrational clinical trials of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections: update from the Biomarkers Consortium of the Foundation for the National Institutes of Health. Clin Infect Dis. 2012;55:1114-21.
5. Bruun T, Oppegaard O, Hufthammer KO, Langeland N, Skrede S. Early response in cellulitis: a prospective study of dynamics and predictors. Clin Infect Dis. 2016;63:1034-41.
6. Reinbolt RE, Shenk AM, White PH, and Navari RM. Symptomatic treatment of infections in patients with advanced cancer receiving hospice care. J Pain Symptom Manage. 2005;30:175-82.
7. White PJ, Kuhlenschmidt HL, Vancura BG, and Navari RM. Antimicrobial use in patients with advanced cancer receiving hospice care. J Pain Symptom Manage. 2003;25:438-43.
8. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:147-59.
9. Moran GJ, Krishnadasan A, Mower WR, Abrahamian FM, LoVecchio F, Steele MT, et al. Effect of cephalexin plus trimethoprim-sulfamethoxazole vs cephalexin alone on clinical cure of uncomplicated cellulitis: a randomized clinical trial. JAMA. 2017;317:2088-96.
10. Pallin DJ, Binder WD, Allen MB, Lederman M, Parmar S, Filbin MR, et al. Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole versus cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. Clin Infect Dis. 2013;56:1754-62.
11. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis. 2008;47:735-43.
12. Miller LG, Daum RS, Creech CB, Young D, Downing MD, Eells SJ, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. N Engl J Med. 2015;372:1093-103.
13. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52:e18-55.
14. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. Pediatrics. 2005;115:1048-57.
15. Walters-Kluwer 2019, Lexicomp Interaction Monograph lisinopril-sulfamethoxazole/trimethoprim.
16. Fahimi J, Singh A, Frazee BW. The role of adjunctive antibiotics in the treatment of skin and soft tissue abscesses: a systematic review and meta-analysis. CJEM. 2015;17:420-32.
17. Singer AJ, Thode HC Jr. Systemic antibiotics after incision and drainage of simple abscesses: a meta-analysis. Emerg Med J. 2014;31:576-8.
18. Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Arch Intern Med. 2004;164:1669-74.
19. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54:e132-73.
20. Ammerlaan HS, Kluytmans JA, Wertheim HF, Nouwen JL, Bonten MJ. Eradication of methicillin-resistant Staphylococcus aureus carriage: a systematic review. Clin Infect Dis. 2009;48:922-30.
21. Workowski KA and Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1-137.
22. Lexicomp Online, Lexi-Drugs Online; Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020.
23. Sanford Guide to Antimicrobial Therapy, Sanford Guide Collection App; Sperryville, Virginia: Antimicrobial Therapy, Inc.; 2020.
24. Selva Olid A, et al. Systemic antibiotics for treating diabetic foot infections (Review). Cochrane Database of Systematic Reviews. 2015;9:CD009061.
25. Earl P, Sisson PR, Ingham HR. Twelve-hourly dosage schedule for oral and intravenous metronidazole. J Antimicrob Chemother. 1989;23(4):619-621.

Skin & Soft Tissue Infections - Fungal

DEFINITION

- **Yeasts** are fungal organisms which commonly colonize the skin and gastrointestinal tract, but may cause skin infection in patients with skin breakdown, poor hygiene, or immunocompromise.
- **Dermatophytes** are molds causing superficial skin infections and include *Trichophyton*, *Epidermophyton*, and *Microsporum* species.[1]

ETIOLOGY, RISK FACTORS, AND DIAGNOSIS

- Most often result from prolonged exposure to moisture but can also be acquired from the environment, especially in immunocompromised patients[2]
  - » Hospice patients are often debilitated and commonly experience a hygienic decline that increases risk of developing fungal infections.
- Typically appear as a raised rash that can cause intense itching, burning, pain and discomfort.
  - » Distinguishing between fungal / bacterial SSTI
    - ° Fungal lesions have raised margins and a scaled pattern.
    - ° The center of dermatophyte lesions is generally less inflamed than the edges.
- Commonly caused by yeast, such as *Candida* spp. or *Malassezia furfur*, or dermatophytes
- However, it is unlikely to know the exact causative organism of a fungal infection, so other factors like the appearance and location of the infection should be considered in order to determine the most likely cause and select the most appropriate therapy.[1]
  - » Fungal infections are commonly found in intertriginous folds, which include the areas under the breasts, the groin, and between the digits of the hands and feet.[2]
  - » *Candida* infection should be suspected if a rash develops in a high moisture area such as the groin.[3]
  - » Examples of dermatophyte SSTIs include tinea pedis ("athlete's foot"), tinea cruris (an infection of the upper thighs or buttock, "jock itch"), and tinea corporis (ringworm).[2] Location and appearance need to be considered when diagnosing; for example:
    - ° Patients with interdigital pruritus who complain of severe itching may suggest that they have tinea pedis, or athlete's foot.
    - ° A patient who develops a circular, red, lesion after the introduction of a new cat into the household may have been infected with tinea corporis, or ringworm.
  - » Dermatophytes may also cause fungal infections of the nails (onychomycosis), whereby the nails become thickened and brown, yellow, or white in color.
- The presence of fungal infections usually reduces the quality of life, so treatment should be commenced in hospice patients when consistent with goals of care.

CLINICAL INSIGHTS

ANTIFUNGAL THERAPY

- Affected areas should be kept dry and clean.
- Topical antifungal agents are utilized as first-line treatment options to provide symptomatic relief and resolve the infection.[2]
  - » Limited information exists with regards to the comparative efficacy between topical antifungals, but several meta-analyses have concluded that all are superior to placebo.[4]
- Co-prescribing topical steroids should be avoided unless necessary to control itching
- Cutaneous candidiasis
  - » Standard treatment duration is 2-4 weeks
  - » There is a lack of literature comparing the topical antifungal agents available for this indication.
  - » Nystatin has activity against *Candida* and is the most commonly used antifungal drug in the hospice setting.
  - » Traditional imidazole antifungal agents like clotrimazole and miconazole are also effective, but newer imidazoles such as sulconazole, oxiconazole, and luliconazole are more expensive and may be less effective against *Candida*.[1]
  - » Although not commonly used in the hospice setting, ciclopirox is a broad-spectrum topical antifungal agent that has activity against *Candida*, as well as all dermatophytes and tinea versicolor.
  - » Terbinafine can be used to treat *Candida*, but it is less effective than the above agents.[1]

- » Tolnaftate should not be used for *Candida* infections.

- Dermatophyte infection
  - » Topical antifungal therapy is preferred over systemic treatments when possible.
    - ° Terbinafine or imidazole therapy (e.g. miconazole, clotrimazole) for 1-4 weeks
  - » Large lesions and infections of the nail generally require oral therapy.
    - ° Terbinafine, fluconazole, or itraconazole are most commonly used.
    - ° Terbinafine may be more active than itraconazole for toenail infection due its ability to concentrate within the nail tissues.[5]
    - ° The standard duration of treatment for fingernail infection is 6 weeks, with extended treatment courses (12 weeks) required for toenail infections due to the slower growth rate of toenails versus fingernails.
    - ° Given the low cure rates (~30-60%), long treatment durations, and risks for adverse effects and drug interactions, the risks and benefits of antifungal therapy should be carefully weighed before initiating treatment for nail infection.
      - › The mean and median lengths of stay of hospice patients are 71 days and 24 days, respectively. As such, many hospice patients would not live to realize infection resolution.[6]
    - ° Direct application of 100% tea tree oil to infected nails is an alternative to antifungal therapy, with similar response rates to traditional antifungals.[7]

FORMULATION CONSIDERATIONS

- Ointments
  - » Ointments have an oil base, and are more slowly absorbed into the skin than creams.
  - » May be preferred for dry, scaly lesions, as they can help to keep the skin moist for longer periods
  - » Generally contain fewer preservatives than creams, and may be better tolerated by patients prone to local skin reactions
  - » Difficult to wash off and may stain clothing
- Creams
  - » Creams have a water base and are more rapidly absorbed into the skin.
  - » Generally preferred by patients, as they are less heavy/sticky compared to ointments
  - » May be preferred for larger infected areas, as they may be easier to spread across more expansive areas of skin
  - » May be preferred for oozing or moist skin lesions, as they tend to have a drying effect
- In general, there are trends between topical agents' indication(s) and the corresponding preferred formulation.[8]
  - » *Candida* infections often have recommendations for a cream formulation, but if the infection is in a high moisture area, then a powder or ointment is the preferred formulation.
  - » The preferred formulation for the treatment of ringworm or tinea cruris is also a cream formulation.
  - » The treatment of onychomycosis usually utilizes a solution or oral antifungal.
  - » Lotions or shampoos are generally preferred if the affected areas have hair and/or are areas with seborrhea, as seen with a tinea versicolor infection.[3]
  - » With interdigital fungal infections, there is a wide variety of recommended formulations which include creams, foams, solutions, aerosols and gels.
    - ° In this instance, other factors such as the desired agent, level of moisture in the affected area, and patient preference should be considered.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
POLYENE ANTIFUNGAL[8]				
Nystatin (Nyamyc)	Apply Q8-12H to affected area until healing is complete	Cream: 100,000units/g Ointment: 100,000units/g Powder: 100,000units/g	• Only indicated for *Candida*	N/A
IMIDAZOLE ANTIFUNGALS[8]				
Clotrimazole (Lotrimin)	Apply Q12H to affected area X 2-4 weeks	Cream: 1% Ointment: 1% Topical Solution: 1%	• Indicated for *Candida*, tinea versicolor, dermatophytes • Available OTC	N/A
Ketoconazole (Extina, Nizoral, Xolegel)	Apply Q24H to affected area and surrounding area X 2-6 weeks	Cream: 2% Foam: 2% Gel: 2% Shampoo: 1%	• Indicated for *Candida*, dermatophytes, tinea versicolor, dandruff, seborrheic dermatitis • Some preparations available OTC • Oral formulation also available, but should be avoided due to strong CYP 3A4 inhibition and increased adverse effects versus alternative oral azoles • Leave shampoo on hair/scalp for 3 minutes; rinse shampoo with cool water to limit systemic absorption • Shampoo may cause permanent changes in hair texture	N/A
Miconazole (Micaderm)	Apply Q12H to affected area X 2-4 weeks	Cream: 2% Ointment: 2% Powder: 2% Powder (aerosol): 2% Spray (aerosol): 2% Topical Solution: 2%	• Indicated for *Candida*, dermatophytes • Available OTC • May cause local skin irritation and burning	N/A

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
TRIAZOLE ANTIFUNGALS [1, 2, 5, 8, 9]				
Fluconazole (Diflucan)	Candida: 150mg once weekly X 4 weeks Tinea: 150-300mg PO once weekly X 2-6 weeks Onychomycosis: 150-200mg PO daily or once weekly X 12 weeks	Oral Suspension: 50mg/5ml, 200mg/5ml Tablet: 50mg, 100mg, 150mg, 200mg	• Alternative oral therapy for *Candida*, dermatophytes, or onychomycosis • Drug-drug interactions (risk increases with higher doses): CYP 2C9 and CYP 3A4 inhibition • Rare hepatotoxicity • Requires renal adjustments with daily administration	Y
Itraconazole (Sporanox)	100-200mg PO Q24H X 2-4 weeks Onychomycosis (fingernails only): 200mg PO Q12H X 1 week; repeat 1-week course after 3-week off-time Onychomycosis (toenails): 200mg PO Q24H X 12 weeks	Capsule: 65mg, 100mg Oral Solution: 10mg/ml	• Alternative oral therapy for *Candida* or onychomycosis • Capsule formulation requires acid for absorption; absorption poor compared to solution even when optimized • Drug-drug interactions: CYP 3A4 inhibition • Rare hepatotoxicity (consider transaminase monitoring with courses >21 days) • Negative inotrope (use cautiously in heart failure)	N

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER ANTIFUNGALS[8]				
Ciclopirox (Ciclodan)	Apply Q12H to affected area and surrounding skin X 4 weeks Onychomycosis: Apply solution to affected nails Q24H X 12 weeks	Cream: 0.77% Gel: 0.77% Shampoo: 1% Topical Solution: 8% Topical Suspension: 0.77%	• Indicated for *Candida*, dermatophytes, interdigital tinea corporis or tinea pedis, onychomycosis (with oral therapy or if oral therapy not tolerated), seborrheic dermatitis • Shake suspension well before use • Leave shampoo on hair/scalp for 3 minutes; rinse shampoo with cool water to limit systemic absorption and prevent tachycardia • Do not apply nail solution to uninfected nails • Remove solution from nails with alcohol every 7 days	N/A
Terbinafine (Lamisil)	Topical: Apply to affected area Q24H X 1-2 weeks Fingernail infection: 250mg PO Q24H X 6 weeks Toenail infection: 250mg PO Q24H X 12 weeks	Cream: 1% Spray: 1% Tablet: 250mg	• Preferred oral therapy for onychomycosis, some *Candida* activity • Available OTC • May cause local irritation • Rare hepatic dysfunction	Y
Tolnaftate (Tinactin)	Apply Q12H to affected area X 2-4 weeks	Cream: 1% Powder (aerosol): 1% Powder: 1% Spray (aerosol): 1% Topical Solution: 1%	• Indicated for tinea pedis, tinea corporis, and tinea cruris • Available OTC • May cause local irritation	N/A

References

1. Goldstein AO, Goldstein BG. Dermatophyte (tinea) infections. In: Dellavalle R, ed. UpToDate. Waltham, Mass.: UpToDate; 2019. www.uptodate.com. Accessed February 20, 2019.
2. Brown TR, Dresser LD. Superficial Fungal Infections. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146073021. Accessed February 19, 2019.
3. Weinstein A, Berman B. Topical treatment of common superficial tinea infections. Am Fam Physician. 2002;65:2095-103.
4. Rotta, I, Otuki, MF, Sanches AC, et al. Efficacy of topical antifungal drugs in different dermatomycoses: a systematic review with meta-analysis. Rev Assoc Med Bras. 2012; 58:308-18.
5. Kreijkamp-Kaspers S, Hawke K, Guo L, et al. Oral antifungal medication for toenail onychomycosis. Cochrane Database Syst Rev. 2017;7:CD010031.
6. National Hospice and Palliative Care Organization, Facts and Figures – Hospice Care in America, 2017 ed. Revised April 2018; accessed online May 2019 at: https://www.nhpco.org/sites/default/files/public/Statistics_Research/2017_Facts_Figures.pdf
7. Buck DS, Nidorf DM, Addino JG. Comparison of two topical preparations for the treatment of onychomycosis: Melaleuca alternifolia (tea tree) oil and clotrimazole. J Fam Pract. 1994;38:601-5.
8. Lexi-Drugs Online. Hudson, OH: Lexi-Comp Inc.; http://online.lexi.com.
9. Scher RK, Breneman D, et al. Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungal onychomycosis of the toenail. American Academy of Dermatology. 1998;38(6):S77-S86.

Thrush
(oropharyngeal candidiasis)

DEFINITION

Oropharyngeal candidiasis or "thrush" is a localized mucocutaneous infection caused by yeast (*Candida* species) and affecting the tongue and other mucous membranes.

ETIOLOGY AND RISK FACTORS

- *Candida albicans*, a common commensal organism within the gastrointestinal tract, including the oral cavity, is responsible for the vast majority of cases.
- Non-albicans *Candida* species have gradually emerged as potential organisms in refractory or multiple repeated candidiasis episodes, with the likelihood increasing among patients with long-term exposures to azole antifungal therapy.[1]
- The presence of mucocutaneous candidiasis is a marker of immune suppression, with risk factors including:
  - » HIV (particularly CD4 cell counts < 200-300 cells/μL)[1]
  - » Leukemia and other cancers
  - » Radiation therapy
  - » Steroid therapy (including the use of inhaled corticosteroids for chronic respiratory disease, particularly when proper technique with thorough mouth rinsing is not followed)[2, 3]
  - » Diabetes (relative immune suppression and increased *Candida* colonization)
  - » Antimicrobial therapy (increased *Candida* colonization)
  - » Denture use (source of mucosal inflammation and epithelial thinning under the dental plates)
- Patients with mucocutaneous candidiasis may also have esophageal involvement (esophageal candidiasis), which is generally associated with more severe immune suppression (eg. CD4 < 50 cells/μL) and may require more aggressive treatment.
  - » Occasionally patients with esophageal candidiasis may not have concomitant oropharyngeal candidiasis.

DIAGNOSIS

- Oropharyngeal candidiasis is clinically characterized by the presence of distinctive painless, creamy white ("cottage cheese"), plaque-like lesions.
  - » These lesions are pseudomembranes composed of *Candida*, epithelial cells, and necrotic tissue, and potentially food debris, keratin, and bacteria.
  - » They are easily removable by scraping using a tongue depressor or other instrument. Of note, this distinguishes these lesions from oral hairy leukoplakia lesions, a potential virus-associated condition in patients with HIV, which are non-removable.
- Angular cheilitis, which is redness and crusting around the corners of the mouth with associated inflammation, may also be present.
- Common patient complaints include painful chewing or swallowing, which can present as loss of appetite, as well as taste distortions, including a "cotton-like" taste; however, oropharyngeal candidiasis can also be asymptomatic.[4]
- Generally, the presence of signs and symptoms of oropharyngeal candidiasis is sufficient for diagnosis and further workup is not needed.
  - » Culturing of lesions is rarely indicated unless susceptibility testing is desired to assess if antifungal resistance is present.
- Esophageal involvement may be suspected with additional symptoms of substernal chest pain, chronic nausea, or discomfort when swallowing.
  - » For esophageal candidiasis, endoscopy is required for definitive diagnosis, but a presumptive diagnosis may be made with the presence of oral lesions in conjunction with esophageal symptoms, particularly in hospice patients where this workup is not practical.

CLINICAL INSIGHTS

- Oropharyngeal candidiasis is treated with topical or oral antifungal therapy, typically for 7-14 days.
- Topical antifungals commonly used to treat oropharyngeal candidiasis treatment include nystatin suspension, clotrimazole troches, or miconazole buccal tablets.
  - » Advantages of topical antifungals:
    - ° Well-tolerated and avoid drug-drug interactions
    - ° Patients with angular cheilitis may benefit from additional application of topical clotrimazole or miconazole cream to the inflamed area.

- For patients with dentures, soaking the denture cup with nystatin suspension for 24 hours may also help to eradicate any fungal colonization.[5]

» Disadvantages of topical antifungals

- Frequent dosing – all but miconazole require 4-5x daily dosing
- Time – nystatin suspension should be swished and retained for several minutes and it takes about 30 minutes for lozenges / troches to dissolve
- Some patients may have insufficient strength to swish and retain nystatin suspension for the desired time period (several minutes); clotrimazole or miconazole may be preferred for these patients.[5]
- Troche / lozenge dosage forms may be choking hazards for some patients

» Topical antifungals should not be used if esophageal candidiasis is suspected.

- Oral fluconazole is often reserved for more serious infections or for use in immunocompromised patients.
  - » Usually required in cases with esophageal involvement where higher doses and longer treatment durations (2-3 weeks) are required
  - » Preferred treatment for patients with HIV, as it is associated with reduced rates of relapse compared to topical agents[2]
  - » Recommended first-line for patients with cancer-related infection or neutropenia[6]
  - » Fluconazole inhibits CYP2C9 and CYP3A4 metabolism, which may result in increased INR values for patients receiving warfarin therapy, as well as many other drug interactions.
  - » Although the efficacy of single-dose fluconazole therapy[7, 8] has been explored, this strategy is not endorsed by recent clinical guidelines.[1, 2, 6]
- For patients whose symptoms of esophagitis do not resolve with empiric antifungal treatment, differential diagnoses including radiation esophagitis, reflux, cytomegalovirus, or herpes simplex virus infection should be considered.
- Mucocutaneous candidiasis refractory to standard fluconazole treatment is rare (<5%)[1], however in this circumstance larger doses of fluconazole (up to 800mg daily in adults with normal renal function)[9] or an alternative oral azole (eg. itraconazole, voriconazole, posaconazole, or isavuconazole) may be considered.
  - » As initial treatment of fluconazole-refractory infection, itraconazole solution is preferred among these options for both oropharyngeal and esophageal candidiasis, as it has a narrower spectrum of antifungal activity and high (up to 80%) response rates for this indication.[2]

PREVENTION AND SUPPRESSIVE THERAPY

- Primary antifungal prophylaxis against mucocutaneous candidiasis is not indicated in hospice patients given the condition's low mortality, the high effectiveness of acute treatment, the potential for adverse drug effects and antifungal resistance development[10], unnecessary drug costs and administration burdens.
- For the same reasons, secondary prophylaxis is also not routinely recommended, but may be considered for patients with severe and frequent recurrences when the recurrences are having a significant negative effect on the patient's well-being and quality of life.
  - » Frequent recurrences are most commonly seen among patients with HIV and low CD4 counts (< 200 cells/μL).[1]
- For patients with HIV, active antiretroviral therapy promotes immune reconstitution, decreases oral *Candida* colonization, and reduces the incidence of recurrent infection.
- For candidiasis associated with denture use, promotion of oral hygiene and disinfection of the dentures is strongly recommended as adjunctive treatment and for recurrence prevention, and ill-fitting plates should be corrected.[2]
- Although some natural products, including tea tree oil, demonstrate in vitro activity against *Candida* species, there is insufficient evidence to recommend their use in oropharyngeal candidiasis prevention at this time.[11 – 13]

ANTICIPATED TREATMENT BENEFIT

- The purpose of drug treatment is to improve associated signs and symptoms.
- For oropharyngeal candidiasis, treatment response is anticipated within 2-3 days. For esophageal candidiasis, symptomatic response may be delayed, with some improvement expected by day 7.
- Treatment is virtually always indicated for esophageal candidiasis, given the more significant symptom burden and potential progression to ulceration.[1] Treatment is also recommended for oropharyngeal candidiasis, however it should be recognized that the symptomatic benefits of antifungal therapy have been inconsistently observed among the hospice population.[3, 14]
- While antifungal treatment is generally advised, there may be individual circumstances where the risks of antifungal therapy outweigh the benefits, and it may be reasonable to withhold therapy in this circumstance (eg. actively dying).

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Clotrimazole (Mycelex)[2, 15]	Oropharyngeal candidiasis: 10mg PO 5 times daily X 7-14 days Prophylaxis/ suppression: 10mg PO Q8H	Lozenge/ troche: 10mg	• Do not use if esophageal involvement suspected • Let troche/lozenge melt slowly in mouth, do not chew or swallow. Time to dissolve is about 30 min. • Potential cutaneous hypersensitivity (rash and pruritus)	N
Fluconazole (Diflucan)[2, 9, 15, 16]	Oropharyngeal candidiasis: 200mg loading dose PO once then 100mg PO Q24H X 7-14 days or 150mg PO x 1 dose Esophageal candidiasis: 400mg loading dose PO once then 200mg PO Q24H X 14-21 days Refractory oropharyngeal or esophageal candidiasis (max dose): 800mg PO Q24H X 14-28 days Prophylaxis/ suppression: 100mg PO 3 times weekly	Oral Suspension: 50mg/5ml, 200mg/5ml Tablet: 50mg, 100mg, 150mg, 200mg	• Preferred therapy for patients with HIV or cancer • Loading dose optional and can help with coverage until steady state is reached • Drug-drug interactions (risk increases with higher doses): CYP2C9 and CYP3A4 inhibition • Rare hepatotoxicity • Requires renal adjustment; decrease dose by 50% if CrCl < 50ml/min • Single-dose regimens may be associated with increased relapse rates in patients with HIV	Y
Itraconazole (Sporanox)[2, 15]	Oropharyngeal candidiasis (fluconazole-refractory): 200mg PO Q24H X 7-28 days Esophageal candidiasis (fluconazole-refractory): 200mg PO Q24H X 14-28 days	Oral Solution: 10mg/ml	• Only recommended for fluconazole-intolerant patients or refractory disease • Capsule formulation also available, but not recommended for this indication due to reduced efficacy and absorption • Drug-drug interactions: CYP3A4 inhibition • Hepatotoxicity is a rare, but serious side effect; risk increases with extended courses • Negative inotrope (use cautiously in heart failure) • Expensive	N/A

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Miconazole (Oravig)[15]	Oropharyngeal candidiasis: 50mg buccally Q24H X 7-14 days	Tablet (buccal): 50mg	• Primary advantage is once-daily dosing • Do not use if esophageal involvement suspected • After brushing teeth in AM, place in the upper gum over the canine tooth and leave to dissolve. Alternate side of mouth with each dose. • Potential cutaneous hypersensitivity (rash and pruritus) • Expensive	N
Nystatin[2, 15]	Oropharyngeal candidiasis: 500,000 units (range 400,000-600,000) PO Q6H X 7-14 days	Oral Suspension: 100,000 units/ml	• Swish suspension in mouth and retain for as long as possible (at least several minutes) before swallowing • Do not use if esophageal involvement suspected • Potential cutaneous hypersensitivity (rash and pruritus) and bitter taste	N/A

References

1. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed Apr 14, 2019. 152-160.
2. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:e1-50.
3. Reinbolt RE, Shenk AM, White PH, and Navari RM. Symptomatic treatment of infections in patients with advanced cancer receiving hospice care. J Pain Symptom Manage. 2005;30:175-82.
4. Thompson GR 3rd, Patel PK, Kirkpatrick WR, Westbrook SD, Berg D, Erlandsen J, et al. Oropharyngeal candidiasis in the era of antiretroviral therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109:488-95.
5. McPherson ML, Kim M, Walker KA. 50 practical medication tips at end of life. J Support Oncol. 2012;10:222-9.
6. National Comprehensive Cancer Network. Prevention and treatment of cancer-related infection. (Version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed April 18, 2019.
7. Hamza OJ, Matee MI, Brüggemann RJ, Moshi MJ, Simon EN, Mugusi F, et al. Single-dose fluconazole versus standard 2-week therapy for oropharyngeal candidiasis in HIV-infected patients: a randomized, double-blind, double-dummy trial. Clin Infect Dis. 2008;47:1270-6.
8. Lagman R, Davis M, LeGrand S, et al. Single-Dose Fluconazole Therapy for Oral Thrush in Hospice and Palliative Medicine Patients. Am J Hosp Palliat Care. 2017;34(7):645-649.
9. Vazquez JA. Optimal management of oropharyngeal and esophageal candidiasis in patients living with HIV infection. HIV AIDS (Auckl). 2010;2:89-101
10. Revankar SG, Kirkpatrick WR, McAtee RK, Dib OP, Fothergill AW, Redding SW, et al. A randomized trial of continuous or intermittent therapy with fluconazole for oropharyngeal candidiasis in HIV-infected patients: clinical outcomes and development of fluconazole resistance. Am J Med. 1998;105:7-11.
11. Ninomiya K, Maruyama N, Inoue S, Ishibashi H, Takizawa T, Oshima H, et al. The essential oil of Melaleuca alternifolia (tea tree oil) and its main component, terpinen-4-ol protect mice from experimental oral candidiasis. Biol Pharm Bull. 2012;35:861-5.
12. Bagg J, Jackson MS, Petrina Sweeney M, Ramage G, Davies AN. Susceptibility to Melaleuca alternifolia (tea tree) oil of yeasts isolated from the mouths of patients with advanced cancer. Oral Oncol. 2006;42:487-92.
13. Soukoulis S, Hirsch R. The effects of a tea tree oil-containing gel on plaque and chronic gingivitis. Aust Dent J. 2004;49:78-83.
14. White PJ, Kuhlenschmidt HL, Vancura BG, and Navari RM. Antimicrobial use in patients with advanced cancer receiving hospice care. J Pain Symptom Manage. 2003;25:438-43.
15. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020.
16. De Wit S, Goossens H, Clumeck N. Single-dose versus 7 days of fluconazole treatment for oral candidiasis in human immunodeficiency virus-infected patients: a prospective, randomized pilot study, J Infect Dis, 1993, vol. 168 (pg. 1332-3

Urinary Tract Infections

DEFINITION

- **Urinary tract infections (UTIs)** are infections of the urinary tract caused by uropathogens.
- **Uropathogens** are bacteria capable of adhering to the bladder wall and invading urinary tissue to establish infection.
- **Lower UTIs (cystitis)** involve the infection of the bladder only.
- **Upper UTIs (pyelonephritis)** usually involve the kidneys.
- **Bacteriuria** refers to the presence of bacteria in the urine, which may represent UTI or, more commonly, asymptomatic bacteriuria (ASB).
- **Asymptomatic bacteriuria (ASB)** describes bacterial colonization of the bladder without clinical infection or associated symptoms and is present in up to 50% of all long-term care residents.[1]
- **Recurrent UTI** is defined as 2 or more symptomatic UTIs in 6 months or 3 or more in 1 year.

ETIOLOGY AND RISK FACTORS

- Because of the anatomical proximity of the bowel to the urethra, particularly in women, most UTIs occur via the "ascending route," whereby enteric bacteria ascend the urethra to the bladder and, in pyelonephritis, to the kidneys.
- Less commonly, UTI may occur through hematogenous seeding of the kidney from the blood and this is usually associated with a more significant infection such as endocarditis.[2]
- UTIs are predominantly caused by a single bacteria spp. (**Table 1**).

TABLE 1 – UTI PATHOGENS

COMMUNITY ONSET	HEALTHCARE-ASSOCIATED
E. coli (80-95% of cases)	*E. coli* (40% of cases)
Staphylococcus saprophyticus	*Pseudomonas* spp.
Klebsiella spp.	*Klebsiella* spp.
Proteus spp.	*Proteus* spp.
Enterococcus spp. is a very rare cause of community onset except in men with BPH	AmpC-producing Enterobacteriaceae (e.g. *Enterobacter* spp. and *Citrobacter* spp.)
	+/- *Enterococcus* spp.

- *Escherichia coli* is the most common uropathogen, followed by other Enterobacteriaceae.[3]
- *Pseudomonas aeruginosa* and other resistant gram-negative bacteria should be considered in patients with exposures to the healthcare system or who have recently received broad-spectrum antibiotics.[4]
- *Staphylococcus saprophyticus* should be considered for otherwise healthy women.
- *Enterococcus* spp. rarely cause UTI, but should be considered in patients with significant healthcare exposures or other risk factors such as benign prostatic hyperplasia (BPH).
- *Candida* spp. are occasionally isolated from urine, but lack the virulence factors needed to invade bladder tissue and thus should virtually always be dismissed as a colonizer.[5]

RISK FACTORS FOR UTI INCLUDE THE FOLLOWING:

- History of UTI
- Renal transplantation
- Renal obstruction (e.g. kidney stones)
- Urologic instrumentation or surgery
- Diabetes mellitus
- BPH
- Indwelling catheter use
- Renal failure/neurogenic bladder
- Sexual intercourse (including the use of diaphragms and spermicidal jellies)

- Medications:
  - » SGLT-2 inhibitors (e.g. canagliflozin)
  - » Antibiotic treatment of ASB, which eliminates protective commensal ASB bacteria and allows the selective development of new uropathogens which attach to and invade the bladder.[6]
  - » Anticholinergic urinary antispasmodics

DIAGNOSIS

SIGNS AND SYMPTOMS

- UTI diagnosis is established based on patient signs and symptoms (**Table 2**).

TABLE 2 – UTI SYMPTOMS

CYSTITIS SYMPTOMS	PYELONEPHRITIS SYMPTOMS
Dysuria (painful urination)	Dysuria (painful urination)
Frequency	Frequency
Urgency	Urgency
Suprapubic tenderness	Flank pain
	Costovertebral angle tenderness (pain around the area of the back overlying the kidney)

- No minimum number of symptoms are needed to diagnose UTI.
- Urinary symptoms (dysuria, frequency, urgency) are the most specific, particularly dysuria.
- Fever and leukocytosis may or may not be present and are more common among patients with pyelonephritis.
- Cloudy, dark, or foul-smelling urine is usually dependent on hydration status and the concentration of urea in the urine; alone, it is not indicative of a UTI.[7, 8]
- Symptoms in elderly patients may be masked by concomitant conditions causing urgency and incontinence, and pre-existing dementia may limit these patients' ability to self-report urinary symptoms.
- Changes in mental function and other nonspecific signs such as falls, malaise, decreased appetite, and changes in voiding patterns are poorly predictive of UTI[9] and should not be used as the sole basis for establishing a UTI diagnosis in clinically stable patients
  - » Altered mental status is often regarded as a potential indicator of infection, although it should be recognized that there are also numerous known alternative sources of altered mental status in the elderly, including dehydration, hypoxia, and polypharmacy.
  - » Falling was associated with UTI in elderly patients in early studies; however, current evidence indicates no association unless UTI symptoms are also present.[10]
- Patients with indwelling catheters cannot be assessed for dysuria, so should be evaluated for other UTI signs and symptoms such as costovertebral angle tenderness or general indicators of infection before assigning a UTI diagnosis, given virtually all of these patients will have ASB.[11]

URINALYSIS

- Urinalysis (UA) may be used to support a potential diagnosis of UTI, however no component of the UA is diagnostic of UTI on its own due to the inability to distinguish ASB from UTI.
- Leukocyte esterase is a rapid dipstick test used to screen for pyuria (positive test indicates > 10 leukocytes/mm^3).
  - » Virtually all patients with UTI will have pyuria, so its absence can be used to rule out UTI.[12]
  - » Pyuria may also be present with ASB or may be indicative of other diseases such as *Chlamydia trachomatis* and other sexually transmitted infections.[8]
- Nitrite is formed when select bacteria reduce nitrate, and a positive nitrite test indicates bacteriuria with a gram-negative organism.
  - » A positive nitrite test rules out UTI caused by *Enterococcus* spp.
- White cell casts in the urine may indicate kidney damage and thus may potentially implicate pyelonephritis.

- Bacterial counts can be used to rule out UTI, in that bacterial counts of 10^4/ml or less are generally not indicative of infection.
  - » Importantly, higher bacterial counts may still be reflective of ASB rather than infection.
  - » Bacteriuria may not occur with pyelonephritis if a kidney stone is present blocking the infected kidney or if the infected kidney is drained through a nephrostomy tube.

CLINICAL INSIGHTS

ANTICIPATED TREATMENT BENEFIT

- The purpose of antibiotic therapy for UTI is to resolve infection symptoms through eradication of the causative uropathogen while minimizing adverse effects and collateral damage.
- Antibiotic therapy is recommended for symptomatic UTI patients and has been demonstrated to improve UTI symptoms in the majority of patients receiving hospice care (79% symptom response within 72 hours).[13]
- Antibiotic therapy for ASB is not recommended because it increases risk for UTI by eliminating protective commensal bacteria and promotes clonal spread of multi-drug resistant organisms.[6, 14]
- For equivocal UTI cases lacking specific genitourinary symptoms (e.g. altered mental status only), withholding UTI-directed therapy for a period of 24-48 hours is reasonable[15], including for patients with potential catheter-associated UTI.[16]
  - » Fluids or oxygen supplementation alone will often resolve changes in patient mentation.
  - » This "watch and wait" strategy may be preferred from an antibiotic stewardship perspective, but the potential benefits of decreased bacterial resistance and lower UTI rates should be weighed against patient-specific considerations. For example, selecting for resistant bacteria may be less of a concern for a patient with a short anticipated life expectancy given that antibiotic resistance is predominantly a concern for future infections, and it may be reasonable to consider earlier initiation of antibiotic therapy for potential symptom relief and improved end-of-life quality in this circumstance. However, the risks of unnecessarily exposing the patient to potential adverse drug effects, including infectious complications such as *Clostridium difficile*, must be considered as well.

ANTIBIOTIC THERAPY

- Antibiotic therapy for UTI should achieve sufficiently high concentrations in the urine and have adequate activity against the most likely uropathogens using the narrowest-spectrum agent for the shortest effective duration.
- Standard guidelines for treatment may not be applicable when antibiotic resistance patterns in the local community or in individual patients differ from national or regional patterns.
- Effective antibiotic therapy should result in improvement in UTI signs and symptoms within 72 hours.
  - » Patients lacking early clinical response, particularly with immunosuppression, may require longer (10-14 day) treatment courses.[8] However, the potential for antibiotic resistance should be considered and the diagnosis of UTI should also be re-evaluated at this time to assess for complications (e.g. obstruction) and rule out other potential causes of patients' symptoms before extending antibiotic therapy.
- Cystitis
  - » For cystitis in otherwise healthy women, short-course antibiotic therapy with 3 days trimethoprim-sulfamethoxazole (TMP-SMX), 5 days nitrofurantoin, or single-dose fosfomycin is recommended.[3]
  - » Patients with catheter-associated UTI or who are elderly, male, have incomplete bladder emptying, obstructive conditions, or immunodeficiency should generally receive 7 day regimens.[8]
  - » Fosfomycin has demonstrated lower cure rates versus nitrofurantoin[17], however it has an expanded spectrum of activity against extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae and may be preferred if a patient has a known history of ESBL colonization.
  - » In accordance with a 2016 FDA safety review[18], fluoroquinolone therapy should be relegated to second-line status for cystitis treatment, particularly for patients with reduced renal

function, due to increasing resistance[19] and adverse effect risks which include significant altered mental status, peripheral neuropathy, tendonitis, seizures, and QTc interval prolongation.

- Pyelonephritis
  - » Fluoroquinolones remain first-line agents for treatment of pyelonephritis, despite the aforementioned FDA safety review.
    - ° Exception: moxifloxacin is not appropriate for UTI treatment due to inadequate renal elimination.
  - » Neither nitrofurantoin nor fosfomycin have utility in pyelonephritis treatment.
  - » Although guidelines recommend a single intramuscular dose of ceftriaxone or an aminoglycoside when fluoroquinolone therapy is prescribed for pyelonephritis in regions with >10% *E.coli* fluoroquinolone resistance[3], routine use of intramuscular agents is not recommended for hospice patients able to take oral agents due potential injection site pain and bruising or bleeding among patients with thrombocytopenia.
  - » TMP-SMX is an alternative antibiotic for pyelonephritis treatment, though longer treatment durations may be required (7 days for fluoroquinolones versus 14 days for TMP-SMX).[3]
- Drug interactions
  - » Both fluoroquinolones and TMP-SMX may potentially interact with warfarin to increase bleeding risk through multiple mechanisms, though closer INR monitoring should be considered when starting any antibiotic.
  - » Fluoroquinolone antibiotics are susceptible to inactivation and treatment failure when co-administered with metal cations like calcium, aluminum, magnesium, and iron, which are found in significant concentrations in certain foods (e.g., dairy products, nutritional supplements), medications (e.g., aluminum-magnesium hydroxide, magnesium hydroxide), and over-the-counter (OTC) supplements (e.g., calcium, iron, magnesium)
    - ° Administer the fluoroquinolone several hours before or after these products or foods as directed by product labeling.
- Renal dosing considerations
  - » TMP-SMX is generally not recommended in patients with renal failure due to its risk for hyperkalemia[20] and the potential for reduced efficacy in this population, but use may be considered in the absence of other effective treatment options.
    - ° Reducing the doses to single-strength tablets is recommended with CrCl 15-30 ml/min.
  - » Nitrofurantoin should not be used for patients with significant renal impairment (CrCl <30 ml/min)[20] due to inadequate urinary concentrations.
  - » Beta-lactams and fluoroquinolones also require adjustment (see: Symptom guide appendix "Antibiotic Selection with Renal Impairment").
- Oral β-lactams such as cephalexin may be considered for UTI treatment if patient-specific factors contraindicate use of first-line antibiotics; however, these agents are associated with higher relapse rates and may require longer treatment durations (5-7 days for cystitis and 10-14 days for pyelonephritis).[3]

ALTERNATIVE THERAPIES

- Several non-antibacterial therapies have been proposed to aid in UTI treatment, although supporting evidence is weak.
- Forced hydration is generally not recommended.
- Administration of drugs for urinary acidification such as ascorbic acid is also generally not recommended and may cause bladder stones and acidosis.
- Phenazopyridine has been used as adjunctive therapy to relieve symptoms of dysuria, but it has not consistently produced effects in patients with UTIs who were also given antibiotics. However, it may be reasonable to consider the addition of phenazopyridine for patients who previously found benefit with this therapy.
  - » When prescribed, courses should generally not exceed 2-3 days to prevent masking of symptoms of UTI not resolving with antibiotic therapy.
  - » More significant pain should be treated with standard analgesic agents such as acetaminophen.

PREVENTION AND SUPPRESSIVE THERAPY FOR PATIENTS WITH RECURRENT UTI

- Daily low-dose antibiotic prophylaxis appears to be effective in women, including post-menopause, for preventing UTI recurrence, though data among males is lacking.[21]
- Patients with uncorrectable underlying urogenital abnormalities leading to recurrent UTIs are unlikely to benefit from long-term suppressive therapy because treatment merely results in colonization with more resistant organisms while exposing them to adverse drug effects.[22] This is particularly true of chronically catheterized patients.
- For patients requiring catheterization, more effective preventative measures include the preferential use of intermittent catheterization and external (condom) catheters over chronic indwelling catheters to reduce catheter-associated UTI risk.[8, 23] Further, indwelling catheters should be removed as soon as they are no longer needed.
- Nitrofurantoin or TMP-SMX are the most commonly utilized antibiotics for suppressive therapy and have the best evidence for efficacy.
  - » Although well-tolerated as cystitis therapy, the 2019 Beers Criteria recommend against long-term suppressive therapy with nitrofurantoin due to concerns for cumulative hepatic, neurologic, and pulmonary toxicities, though these are potentially less relevant if a patient is terminally ill.[20]
- Methenamine is an antimicrobial agent that degrades in acidic urine to form its active breakdown product, formaldehyde. Urinary pH is < 5.5 is required to facilitate this conversion.
  - » Indicated only as cystitis prophylaxis
  - » Not effective for patients with indwelling catheters because urine is eliminated too rapidly from the body to allow for adequate formaldehyde concentrations
  - » Not as effective at UTI suppression when compared with either TMP-SMX or nitrofurantoin, thus use should be limited to patients unable to tolerate either of these first-line agents[24]
- Cranberry juice or extracts have been proposed to prevent UTI via the anti-bacterial properties of hippuric acid, which is derived from precursors within the berry.
  - » The most updated Cochrane review of 24 randomized controlled trials found that cranberry products did not significantly reduce the incidence of UTI, including when specifically looking at the subgroup of older patients.[25]
  - » Cranberry juice often contains high amounts of sugar, which may be detrimental in diabetic patients.
- D-mannose has also been studied for UTI prevention, with a proposed mechanism of impairing uropathogen adhesion to the bladder wall.
  - » Only D-mannose and α-D-mannose have been shown to have this property *in vitro*; other carbohydrates are not anticipated to have this same anti-adhesive effect.
  - » Few studies have been conducted in humans, thus use is still regarded as investigational. However, in a study of approximately 300 otherwise healthy women with a history of recurrent UTI found that daily D-mannose (2g powder in 200ml water) for 6 months reduced UTI recurrences by 45%, a significant reduction when compared to no prophylaxis and comparable with nitrofurantoin suppression. It currently remains to be seen if these results are reproducible, or applicable to other patient populations with potentially different uropathogen distributions.[26]
  - » D-mannose therapy is well-tolerated, though it may cause diarrhea.[26]

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
FIRST-LINE ANTIBIOTICS [1, 3, 27, 28]				
Ciprofloxacin (Cipro)	Cystitis: IR: 250-500mg PO Q12H X 3 days ER: 500mg PO Q24H X 3 days (Consider 7-day treatment for males) Pyelonephritis: IR: 500mg PO Q12H X 7 days ER: 1,000mg PO Q24H X 7 days Max dose (IR): 750mg PO Q12H	Oral Suspension: 250mg/5ml, 500mg/5ml Tablet: 100mg, 250mg, 500mg, 750mg Tablet (ER)*: 500mg, 1,000mg	**Fluoroquinolones** • First-line agents in pyelonephritis • For cystitis only when first-line agents cannot be used • Cannot substitute moxifloxacin • Consider higher doses for *Pseudomonas* spp. • Multiple potential ADEs, most commonly altered mental status/delirium. Others include photosensitivity, QT prolongation, tendon rupture (rare), and aortic dissection (rare). • Separate antacids and calcium/ iron supplements by several hours on either side of use as directed in product labeling • May increase INR in patients receiving warfarin • Require renal adjustments	Y/N*
Levofloxacin (Levaquin)	Cystitis: 250-500mg PO Q24H X 3 days (Consider 7-day treatment for males) Pyelonephritis: 500mg PO Q24H X 7 days Max dose: 750mg PO Q24H	Oral Solution: 25mg/ml Tablet: 250mg, 500mg, 750mg		Y
Fosfomycin (Monurol)	Cystitis: 3g PO once	Packet: 3g granules for solution	• First-line agent for cystitis if ESBL history • Do not use for pyelonephritis • Dissolve packet contents into 90–120 ml of cool water prior to administration	N/A
Nitrofurantoin (Macrobid/ Macrodantin/ Furadantin)	Cystitis:100mg PO Q12H X 5 days (monohydrate macrocrystal) *OR* 50-100mg PO Q6H x 5 days (macrocrystal or suspension) (Consider 7-day treatment for males) Suppression: 50-100mg PO Q24H (macrocrystal or suspension)	Capsule (macrocrystal): 25mg, 50mg, 100mg Capsule (monohydrate macrocrystal)*: 100mg Oral Suspension: 25mg/5ml	• First-line agent for cystitis • Do not use for pyelonephritis • Do not use with CrCl < 30 ml/min (decreased efficacy) *(Continued on next page)*	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
FIRST-LINE ANTIBIOTICS (CONTINUED)				
Trimethoprim/ Sulfamethoxazole (Bactrim)	Cystitis: 1 DS tablet PO Q12H X 3 days (Consider 7-day treatment for males) Pyelonephritis: 1 DS tablet PO Q12H X 14 days Suppression: ½-1 SS tablet PO Q24H	Oral Suspension: 40/200mg/5ml Tablet: SS: 80/400mg DS:160/800mg	• First-line agent for cystitis • Second-line agent for pyelonephritis • ADRs include photosensitivity, hyperkalemia, and bone marrow suppression (dose-dependent) • Take with fluids to prevent urinary crystallization • May increase INR in patients receiving warfarin via multiple mechanisms • May consider shorter treatment durations for pyelonephritis (7-10 days) with early clinical response • Requires 50% dose adjustment if CrCl < 30ml/min; avoid in patients with ESRD	Y
SECOND-LINE ANTIBIOTICS [1, 3, 27]				
Amoxicillin/ clavulanate (Augmentin)	Cystitis: 500mg PO Q12H X 5-7 days Pyelonephritis: 875mg PO Q12H X 10-14 days	Oral Suspension: 125/31.25mg/5ml, 200/28.5mg/5ml, 250/62.5mg/5ml, 400/57mg/5ml, 600/42.9mg/5ml Tablet: 250/125mg, 500/125mg, 875/125mg Tablet Chewable: 200/28.5mg Tablet (ER)*: 1,000/62.5mg	• For UTI only when first-line agents cannot be used • Increased incidence of diarrhea (take with food) • Do not substitute amoxicillin or ampicillin unless confirmed susceptibility or treating *Enterococcus* spp. • Requires renal adjustments	Y/N*
Cefpodoxime (Vantin)	Cystitis: 100mg PO Q12H X 5-7 days Pyelonephritis: 200mg PO Q12H X 10-14 days	Oral Suspension: 50mg/5ml, 100mg/5ml Tablet: 100mg, 200mg	• For UTI only when first-line agents cannot be used • Other oral cephalosporins may be substituted depending on available formulary agents and uropathogen susceptibility (general activity: 3rd gen > 2nd gen > 1st gen) • Not appropriate for *Serratia* spp., *Providencia* spp, *Morganella* spp., *Citrobacter* spp., or *Enterobacter* spp. even if susceptible due to potential for inducible resistance on therapy • Require renal adjustments	Y
Cephalexin (Keflex)	Cystitis: 500mg PO Q6H X 5-7 days Pyelonephritis: 500mg PO Q6H X 10-14 days	Capsule: 250mg, 500mg, 750mg Oral Suspension: 125/5ml, 250mg/5ml Tablet: 250mg, 500mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
URINARY ANALGESIC[27]				
Phenazopyridine (Pyridium, Azo Urinary Pain Relief)	Dysuria: 200mg (or two OTC tablets) PO TID x 2 days	Tablet (OTC): 99.5mg Tablet (Rx): 100mg, 200mg	• Intended for short-term (2-day) use in conjunction with antibiotic treatment • Causes red/orange discoloration of urine and bodily fluids • Avoid in patients with renal impairment	Y

References

1. Nicolle LE. Urinary tract infections in the older adult. Clin Geriatr Med. 2016;32:523-38.
2. Sobel JD. Pathogenesis of urinary tract infection. Role of host defenses. Infect Dis Clin North Am. 1997;11:531-49.
3. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103-20.
4. Nicolle LE. Complicated urinary tract infection in adults. Can J Infect Dis Med Microbiol. 2005;16:349-60.
5. Kauffman CA, Vazquez JA, Sobel JD, Gallis HA, McKinsey DS, Karchmer AW et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis. 2000;30:14-8.
6. Cai T, Mazzoli S, Mondaini N, Meacci F, Nesi G, D'Elia C, et al. The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: to treat or not to treat? Clin Infect Dis. 2012;55:771-7.
7. Foley A, French L. Urine clarity inaccurate to rule out urinary tract infection in women. J Am Board Fam Med. 2011;24:474–5.
8. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:625-63.
9. Juthani-Mehta M, Quagliarello V, Perrelli E, Towle V, Van Ness PH, Tinetti M. Clinical features to identify urinary tract infection in nursing home residents: a cohort study. J Am Geriatr Soc. 2009;57:963-70.
10. Rowe T, Towle V, Van Ness PH, Juthani-Mehta M. Lack of positive association between falls and bacteriuria plus pyuria in older nursing home residents. J Am Geriatr Soc. 2013;61:653-4.
11. Stark RP, Maki DG. Bacteriuria in the catheterized patient. What quantitative level of bacteriuria is relevant? N Engl J Med. 1984;311:560-4.
12. Stamm WE. Measurement of pyuria and its relation to bacteriuria. Am J Med. 1983;75:53.
13. Reinbolt RE, Shenk AM, White PH, and Navari RM. Symptomatic treatment of infections in patients with advanced cancer receiving hospice care. J Pain Symptom Manage. 2005;30:175-82.
14. Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clin Infect Dis. 2019. [Epub ahead of print]
15. Schulz L, Hoffman RJ, Pothof J, Fox B. Top ten myths regarding the diagnosis and treatment of urinary tract infections. J Emerg Med. 2016;51:25-30.
16. Babich T, Zusman O, Elbaz M, Ben-Zvi H, Paul M, Leibovici L, et al. Empirical antibiotic treatment does not improve outcomes in catheter-associated urinary tract infection: prospective cohort study. Clin Infect Dis. 2017;65:1799-805.
17. Huttner A, Kowalczyk A, Turjeman A, Babich T, Brossier C, Eliakim-Raz N, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial. JAMA. 2018;319:1781-9.
18. FDA Drug Safety Communication. FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. US Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/ucm500143.htm. Accessed Feb 21, 2019.
19. Mohareb AM, Dugas AF, Hsieh YH. Changing epidemiology and management of infectious diseases in US EDs. Am J Emerg Med. 2016;34:1059-65.
20. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67:674-94.
21. Ahmed H, Davies F, Francis N, Farewell D, Butler C, Paranjothy S. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials. BMJ Open. 2017;7:e015233.
22. Rubin RH, Cotran RS, Tolkoff-Rubin NE. Urinary tract infection, pyelonephritis, and reflux nephropathy. In: Brenner BM, ed. Brenner and Rector's The Kidney, 5th ed. Philadelphia: W.B. Saunders, 1997; 1597-654.
23. Saint S, Kaufman SR, Rogers MA, Baker PD, Ossenkop K, Lipsky BA. Condom versus indwelling urinary catheters: a randomized trial. J Am Geriatr Soc. 2006;54:1055-61.
24. Brumfitt W, Cooper J, Hamilton-Miller JM. Prevention of recurrent urinary infections in women: a comparative trial between nitrofurantoin and methenamine hippurate. J Urol. 1981;126:71-4.
25. Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev. 2012;10:CD001321.
26. Kranjcec B, Papes D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. World J Urol. 2014;32:79-84.
27. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020.
28. Lichtenberger P, Hooton TM. Antimicrobial prophylaxis in women with recurrent urinary tract infections. Int J Antimicrob Agents. 2011;38 Suppl:36-41.

DEFINITIONS

Parkinson disease (PD) is a neurodegenerative disorder that predominately affects dopaminergic neurons in the area of the brain called the substantia nigra, resulting in the insidious development of both motor and non-motor symptoms.[1]

On refers to a state in which PD patients are experiencing suppression of PD symptoms through drug therapy.

Off refers to a state in which symptoms of PD are present and not adequately suppressed by drug therapy.

Motor symptoms are movement-related symptoms due to PD (**Table 1**).

Non-motor symptoms are symptoms of PD that are unrelated to movement (**Table 2**).

TABLE 1. MOTOR SYMPTOMS OF PARKINSON DISEASE[1-2]

SYMPTOM	DESCRIPTION
Bradykinesia	Slowness of movement, including in the: • Head – masked facies (hypomimia), soft / breathy / hoarse voice (hypophonia), sialorrhea (drooling) • Trunk – slow initiation of movement, impaired arising from chair / turning on bed, stooped posture, flexed or lateral trunk tilting, instability leading to falls and loss of independence • Limbs – slowness in daily activities, small / cramped handwriting (micrographia), decreased arm swing when walking, short / slow steps with walking (festination), shuffling gait Freezing: feeling stuck in place, unable to initiate movement
Tremor	Mostly at rest and lessens with sleep or using body part
Rigidity	Stiffness in body parts that can cause pain; contributes to masked facies

Motor fluctuations are the return of PD motor symptoms unpredictably or at end of dose as patients move from On to Off; examples include:

- Wearing Off
- Unpredictable Off periods
- Freezing of gait
- Failure of On response
- Acute akinesia (ie, without movement) is an abrupt worsening of PD symptoms that is poorly responsive to drug treatment, can be life threatening, and is usually caused by acute illness, drug administration errors, or use of dopamine blocking drugs (eg, antipsychotics, metoclopramide).[5]

Dyskinesias are involuntary abnormal movements nearly always caused by levodopa that usually occur in the On state; examples include:

- **Peak-dose dyskinesias / choreiform movements** are dance-like, restless, non-rhythmic, jerky movements of the extremities, head, face or trunk that occur when levodopa is at peak concentrations (usually 30-90 minutes after doses).[5]
- **Diphasic dyskinesias** are rare, difficult to manage, and occur twice after each levodopa dose; once as levodopa is taking effect and again as it is losing its effect.[5]
- **Dystonia** is sustained or repetitive muscle twisting, spasms, or cramps that are often painful and usually occur in the Off state (eg, upon wakening as evening/ nighttime medications have worn off) but can also occur while patients are On.[1,5]
- **Akathisia** is restlessness due to dopamine withdrawal or blockade.

Parkinson disease psychosis (PDP) is psychosis occurring in the context of PD and can be due to PD itself, PD drug therapy, or a combination of both.

Impulse control disorders (ICD) include impulsive behaviors like uncontrolled gambling, sex, eating, shopping as well as repetitive, relatively purposeless activities like organizing, sorting, or collecting items (punding).

TABLE 2: NON-MOTOR SYMPTOMS OF PARKINSON DISEASE[1-4]

SYMPTOM	DESCRIPTION / EXAMPLES
Cognitive dysfunction and dementia	Psychomotor retardation, memory difficulty, and altered personality
Mood disorders	Depression: sadness, anhedonia, decreased interest in activities Anxiety: panic disorder, generalized anxiety disorder Apathy: loss of motivation
Psychosis	Hallucinations, delusions
Akathisia	Inner restlessness with constant urge to move and inability to sit still, often displayed as repetitive lower extremity movement, fidgeting while seated, or pacing
Sleep disorders	REM sleep behavior disorder (RBD), insomnia, restless legs syndrome (RLS), sleep fragmentation
Excessive daytime somnolence	Fatigue, sudden sleep attacks
Autonomic dysfunction	Orthostatic hypotension (dizziness, loss of consciousness upon standing), urinary dysfunction (frequency, urgency, and incontinence), delayed gastric emptying, erectile dysfunction
Olfactory dysfunction	Deficits in odor detection (hyposmia) and identification
Pain	Lancinating, burning, or tingling sensations (paresthesias); often feeling of heaviness in large leg muscles during Off periods
Visual disturbances	Dry eyes, reduced blink rate, hallucinations
Dental problems	Burning sensation within the mouth, bruxism
Skin changes	Oily / dry / flaking / inflamed skin, earwax, excessive or diminished sweating

CAUSES

- The causes of PD are not yet fully understood, but they involve both genetic and environmental factors that cause characteristic pathophysiological findings of dopaminergic neuron loss in the substantia nigra portion of the basal ganglia area of the brain as well as Lewy body inclusion into brain neurons.[6-7]

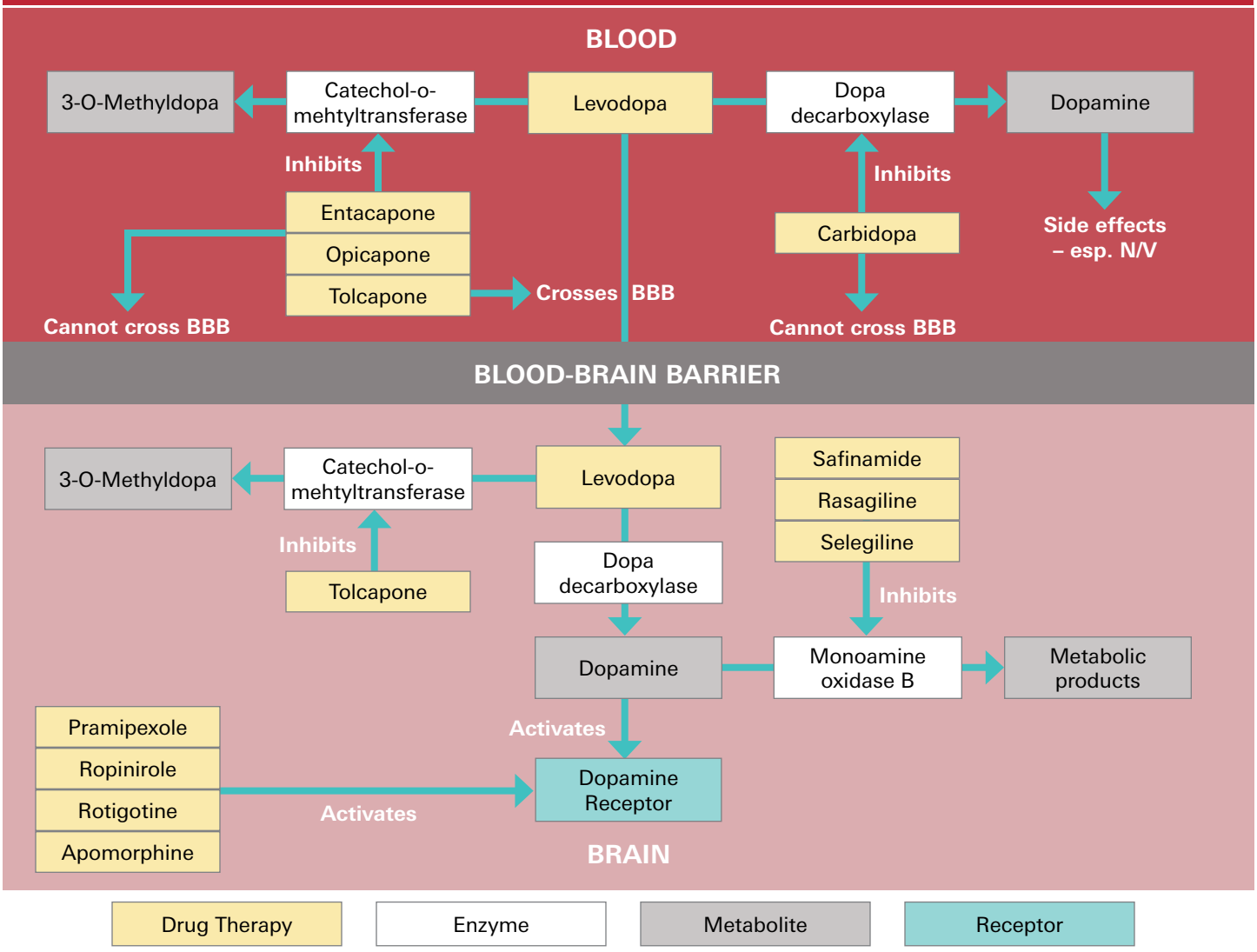
SYMPTOMS

- Motor symptoms of PD include bradykinesia, tremor, and rigidity (**Table 1**).
- Non-motor symptoms of PD (**Table 2**) are less well-known than motor symptoms, but decrease quality of life to a similar extent.

CLINICAL INSIGHTS

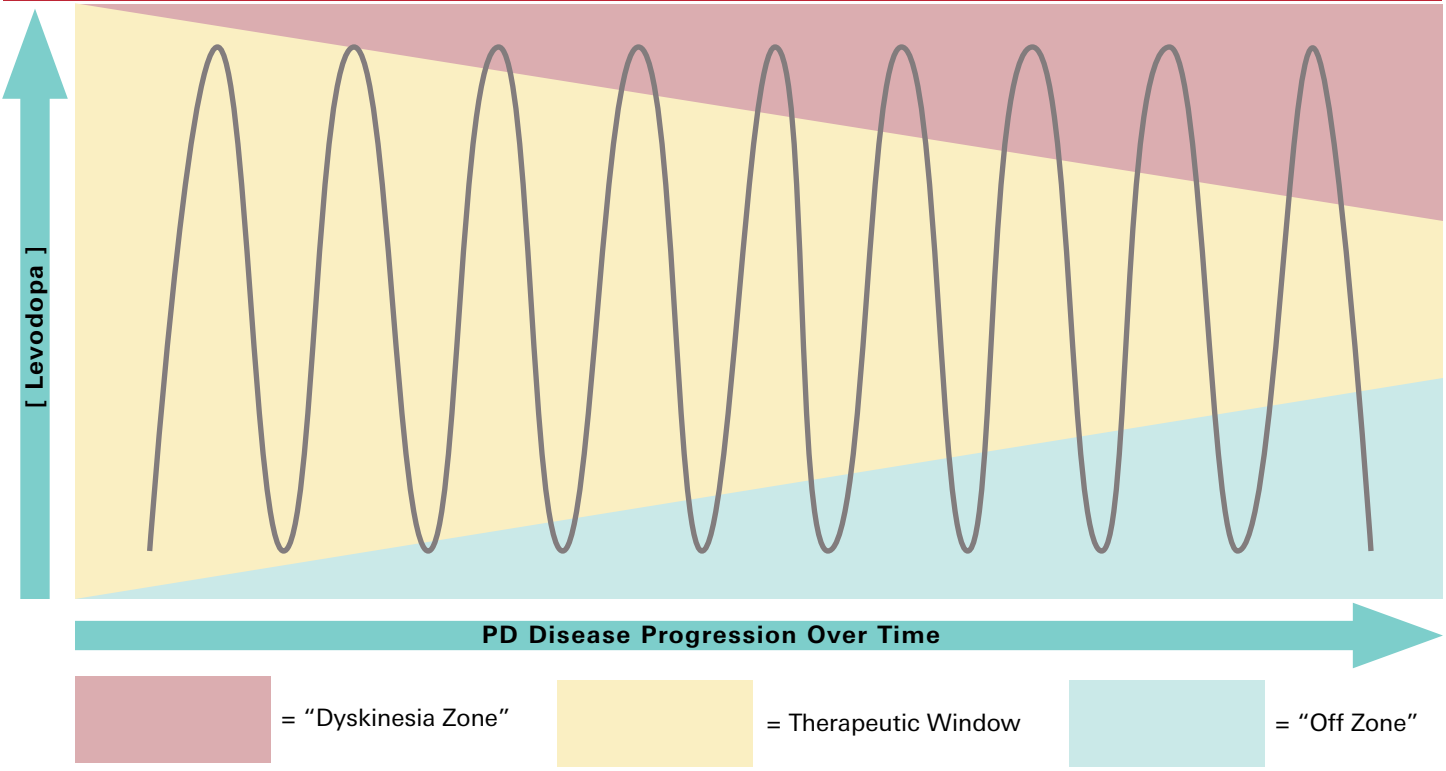
- Most PD patients die from the same causes as age matched individuals without PD; however, those who live with PD for longer periods typically die from PD complications like aspiration pneumonia or fall complications.[4]
- Because PD is incurable and no drugs slow the disease process, all treatments should be considered palliative in nature.[4]
- Other than anticholinergic drugs and amantadine, drug treatment of PD aims to promote dopaminergic effects (**Figure 1**).

FIGURE 1: SCHEMATIC OF PD DRUG THERAPIES THAT PROMOTE DOPAMINERGIC RESPONSE



- With initial treatment, levodopa will often provide around-the-clock suppression of PD symptoms ("long-duration response"), but after years of treatment, levodopa response begins to mirror serum levodopa concentrations ("short-duration response"), exposing most patients to motor fluctuations and dyskinesia (**Figure 2**).
  - » Thought to be due to progressive loss of ability of dopaminergic neurons to store and release dopamine[8]
  - » Motor fluctuations and dyskinesia often persist through the final stages of disease.[9-10]
- Tremor, freezing of gait, and postural instability are less likely to respond to dopaminergic drug treatment than other PD symptoms.[11]
- Levodopa crosses the blood brain barrier via an amino acid transporter that is easily saturated by amino acids from dietary protein. Levodopa-containing drugs are best administered on an empty stomach 30 minutes prior to meals and must be administered at least 1 hour before or 2 hours after meals containing protein. Failure to separate from protein is a common reason for motor fluctuations.[9,12] Consolidating dietary protein to dinner / final meal of the day has been recommended, but overall, dietary protein restriction is not recommended.[13]

FIGURE 2: LEVODOPA RESPONSE OVER TIME



- Motor fluctuation management typically involves increasing dopaminergic drug therapy by one of the following:
  - » Review for levodopa drug / dietary protein interactions and resolve them
  - » More frequent levodopa dosing
  - » Addition of catechol-o-methyltransferase (COMT) inhibitor to prolong levodopa effect
  - » Addition of dopamine agonist or MAO-I
  - » Addition of drugs for acute Off episodes
- It is not necessary to treat non-troublesome dyskinesia and most PD patient prefer dyskinesia to being in the Off state.[9]
- When treatment is required, dyskinesia management typically involves decreasing dopaminergic drug therapy or adding amantadine.
  - » Small studies and case reports indicate that sub-anesthetic ketamine infusions may reduce dyskinesias; it is unknown if other routes of administration would be similarly beneficial. Comorbid depression and/or pain are compelling reasons to consider this therapy.[14]
- Just as motor symptoms may fluctuate with levodopa concentrations and dosing, non-motor symptoms may do so as well. Always review the temporal relationship between symptoms and levodopa administration and corresponding On / Off states (**Table 3**).[8,15]
  - » Up to 80% of PD patients experience insomnia.[16] Subtherapeutic levodopa regimens can cause insomnia due to akathisia, stiffness and patients' inability to turn themselves over; in these cases, an extra levodopa dose can be administered at bedtime.[8,16] Likewise, an extra dose can be administered if / when patients wake in the middle of the night.[8] Melatonin and sedating antidepressants like trazodone or low dose doxepin can be considered as well.[13]
  - » Inadequate levodopa dosing can lead to persistent anxiety. If anxiety is intermittent, it is potentially due to wearing off and short duration levodopa response. Benzodiazepines can be considered, but at the expensive of sedation, decreased cognition, and increased fall risk.[8]

TABLE 3: NON-MOTOR SYMPTOMS THAT MAY FLUCTUATE WITH LEVODOPA DOSING[8,15]

"On" state	Neuropsychiatric	Euphoria, agitation, mania/hypomania, impulses, illusions, psychosis (more likely with non-levodopa PD treatments)
"Off" state	Psychiatric	Anxiety, depression, panic attacks, apathy, fatigue, insomnia, akathisia
	Cognitive	Diminished executive functioning, attention, speech
	Sensory	Pain, paresthesia / numbness
	Autonomic	Urinary symptoms, drooling, sweating, cold extremities, flushing, pallor, fever, dyspnea

- REM sleep behavior disorder (RBD, dream enactment with loss of REM atonia) occurs in about 1 in 4 PD patients (7x higher than non-PD patients) and often precedes PD diagnosis.[16] If treatment is required (ie, patient becomes dangerous, falls out of bed), clonazepam is the preferred treatment. High dose melatonin (6-20mg/night) is less effective, but can be considered if clonazepam is not tolerated or appropriate.[4,8-9,13,16]
- Parkinson disease dementia (PDD) and dementia with Lewy bodies (DLB) are closely related conditions that share common pathophysiology (Lewy body inclusions in brain neurons). Differentiation typically considers the temporal development of symptoms where, PDD is diagnosed if motor symptoms occur prior to cognitive decline and DLB is diagnosed if cognitive symptoms precede motor symptoms.
  - » As with Alzheimer's dementia, cholinesterase inhibitors are used in the treatment of PDD for cognitive preservation, although rivastigmine is the only one with a labeled indication. In addition to the possible modest cognitive benefit, evidence suggests they may also reduce difficult to manage behavioral symptoms in PDD, despite the bulk of clinical evidence suggesting they do not provide similar benefit in other types of dementia.[5,9] Response is unpredictable; they should be deprescribed if no benefit is seen with use.[9]
- When drug treatment is required for Parkinson disease psychosis (PDP), pimavanserin and clozapine are the most effective options, but their use is limited by drug cost and restrictive monitoring requirements, respectively.
  - » Well-tolerated hallucinations / delusions should not be treated.[13]
  - » Quetiapine is of questionable benefit, but is prescribed more often than either pimavanserin or clozapine.[9,17]
  - » Acetylcholinesterase inhibitors may also be beneficial for hallucinations, but not other psychotic symptoms.[9]
- Due to the effects of PD on the autonomic nervous system, neurogenic orthostatic hypotension (nOH) and GI symptoms like nausea, vomiting, constipation, and early satiety can occur.
  - » nOH treatments are discussed elsewhere (see **Cardiovascular Disease – Orthostatic Hypotension** monograph).
  - » Appropriate antiemetics in PD are ondansetron and trimethobenzamide.[1,8,18] Ginger supplements may be beneficial, but interactions with several prescription drug classes are problematic, including increased bleeding if used with anticoagulants and antiplatelets, increased hypoglycemia risk with antidiabetic drugs, and increased hypotension with calcium channel blockers.[1,19]
  - » Supplemental carbidopa given 30 minutes prior to levodopa can be trialed if levodopa-induced nausea / vomiting occurs, however it is expensive and nearly all regimens contain adequate carbidopa (~ 75mg/day effectively blocks peripheral dopa decarboxylase).[9,20]
  - » Constipation is treated as with patients without PD (see **Constipation** monograph).[1]
  - » Delayed gastric emptying affects nearly all PD patients and can significantly affect drug

absorption leading to motor fluctuations and dyskinesias.[21] Erythromycin and/or simethicone can used if gastroparesis causes early satiety / bloating, but metoclopramide is contraindicated.[1,21]

- Depression affects up to half of PD patients; the treatment approach is similar to treating depression in general (see **Depression** monograph).[1]
- Sialorrhea in PD is due to a mishandling of saliva, not overproduction, and can cause embarrassment, halitosis, difficulty with speech, and increased aspiration risk.[21] Anticholinergic drugs can be used if sialorrhea decreases quality of life (see Secretions monograph).[21] Glycopyrrolate is effective and likely preferred due to reduced central anticholinergic effects.[9,21] Botulinum toxin A injections can be considered in severe cases.[13,21]
- ICD treatment involves deprescribing dopamine agonists when possible. Zonisamide, amantadine, topiramate, valproate, quetiapine, clozapine, and naltrexone have shown success in small trials.[9,20]
- Quetiapine and amantadine may reduce punding symptoms.[9]

CONVERSION BETWEEN LEVODOPA DOSAGE FORMS[22-24]

- Nearly all regimens provide adequate carbidopa, so levodopa amount and dosage form-specific bioavailabilities and durations of action are the primary considerations.
- Levodopa bioavailability from orally disintegrating tablets is comparable to that of immediate release (IR) tablets, but bioavailability from extended release tablets is approximately 70-75% that of IR tablets.
- Compared to IR regimens, carbidopa-levodopa extended release capsule (Rytary) regimens can reduce Off time and dyskinesia by as much as 1-2 hours per day when dosed at three times the IR amount of levodopa, but given two-thirds as often.
  - » For example, a regimen consisting of one carbidopa-levodopa 25/100mg immediate release tablet six times daily is approximately equal to three capsules of Rytary 23.75/95mg four times daily.
- If a conversion from an IR / ER tablet regimen to Rytary or another newer dosage form significantly reduced PD symptoms, then backwards conversion to the older regimen solely due to cost / drug formulary status is not recommended.
- All conversions are approximations and close monitoring is essential.

DRUGS TO AVOID IN PD[18]

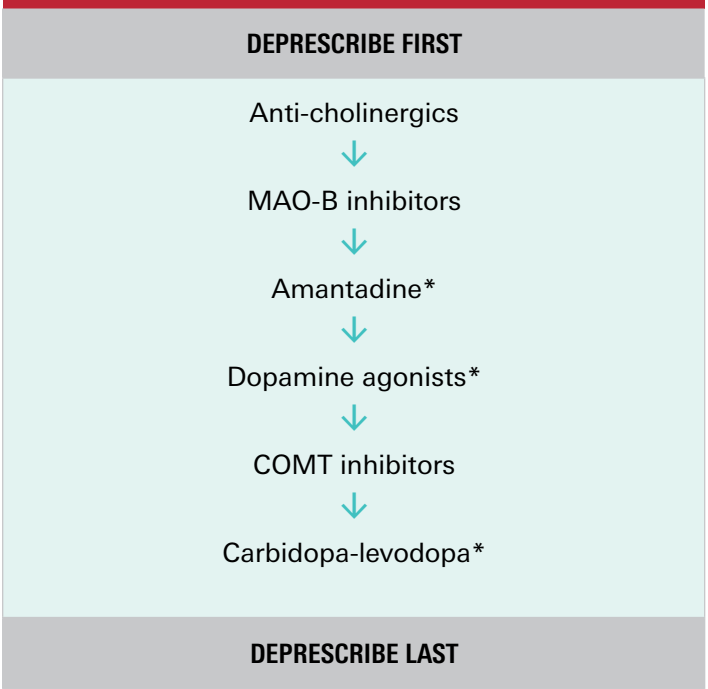
- Medications that block the effects of dopamine at D2 receptors are contraindicated as they worsen PD motor symptoms, blunt intended effects of PD drug therapy, and can cause life-threatening reactions in this population, including neuroleptic malignant syndrome (NMS) and acute akinesia.
- Medications that should be avoided:
  - » 1st generation / "typical" antipsychotics
  - » 2nd generation / "atypical" antipsychotics, except clozapine, quetiapine, pimavanserin[4]
  - » Dopamine-blocking antiemetics: prochlorperazine, metoclopramide, promethazine
  - » Select antihypertensives: reserpine, methyldopa
  - » Select antidepressants: non-selective monoamine oxidase inhibitors (MAOI), amoxapine (tricyclic antidepressant with haloperidol-like metabolite)

DEPRESCRIBING

- Abrupt discontinuation of carbidopa-levodopa can cause clinical deterioration and neuroleptic malignant syndrome, so patients should generally continue preparations as long as they are able to do so.[8]
  - » Patients with a short duration response will typically deteriorate almost immediately after stopping; deterioration is delayed by about 1 week in those with a long duration response.[8]
- Monoamine oxidase B (MAO-B) inhibitors have long half-lives and provide relatively modest benefit, so they may be stopped abruptly if needed.[8]
- COMT inhibitors are also only mildly effective and can be stopped abruptly, including on a trial basis to attempt to lessen levodopa-induced dyskinesias.[8]
- Amantadine is best discontinued by slow taper, especially with long-term (years) use.[8]
- Deprescribing is a critical part of managing Parkinson Disease Psychosis (PDP).[9,17]

  - » Addressing potential drug-induced causes may spare the use of antipsychotic treatment.
  - » First, deprescribe non-PD drugs prone to causing confusion / hallucination, especially anticholinergic drugs used for allergies, insomnia, secretions, incontinence, etc.
  - » Second, withdrawal of PD medications (as tolerated) may be attempted as shown in Figure 3.
- Dose reduction or deprescribing of dopamine agonists is often effective in treating ICDs, though compensatory levodopa increase may be needed. Even with this compensatory increase, up to 20% may experience withdrawal symptoms of anxiety, depression, fatigue, pain, orthostasis, and drug cravings.[9]
- Treatments for acute intermittent Off episodes should be deprescribed if dopamine dysregulation syndrome (DDS, addictive pattern of dopaminergic drug use) occurs.[9]

FIGURE 3: DEPRESCRIBING IN PARKINSON DISEASE PSYCHOSIS



* Taper / avoid abrupt discontinuation

DRUG INFORMATION[22]

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
LEVODOPA-CONTAINING COMBINATION PRODUCTS				
Carbidopa/levodopa (Sinemet, Sinemet CR, Parcopa, Duopa, Rytary)	Initial (ER Capsule): 23.75/95mg PO TID x 3 days, then 36.25/145mg TID Initial (Intestinal suspension): not for initial therapy; initial dose is calculated based on previous oral regimen Initial (Tablet, ODT): 25/100mg PO TID Initial (CR Tablet): 50/200mg PO BID MDD (IR/CR/ODT): Eight tablets per day or not more than 200/2,000mg/day (see notes) MDD (ER Capsule): 612.5/2,450mg/day (see notes) MDD (Intestinal suspension): 100ml (2,000mg levodopa)/ day	Capsule (ER): 23.75/95mg, 36.25/145mg, 48.75/195mg, 61.25/245mg Intestinal suspension: 4.63/20mg/ml Orally Disintegrating Tablet (ODT): 10/100mg, 25/100mg, 25/250mg Tablet: 10/100mg, 25/100mg, 25/250mg Tablet (CR)*: 25/100mg, 50/200mg	• Carbidopa prevents peripheral conversion of levodopa into dopamine, reducing adverse effects and allowing lower doses of levodopa • Adverse effects >10% include: orthostasis, dizziness, headache, nausea/vomiting, dyskinesia, elevated BUN • Tablet MDDs shown are from the package insert, but are relatively arbitrary and based upon studies in mice. Do not limit prescribing or reduce well-tolerated regimens solely due to MDD being exceeded.[8] • Food (especially protein) and iron supplements significantly reduce oral absorption[9,12-13,24] **ER capsules** • Reduce Off time by about 1-2 hours per day more than IR/ER regimens[24] • May be opened if contents are added to applesauce for immediate administration • Expensive **ER tablets** • Notoriously unreliable absorption and kinetics; best reserved as adjunct to IR regimens where HS doses given if dystonia affects sleep[9,13] • Bioavailability ~70-75% of IR tablets **Intestinal suspension** • Requires surgical creation of gastrostomy for catheter, but provides marked reduction in Off time compared to other forms[9] • Patients receive a bolus infusion in the AM, then the infusion runs for the next 16 hours, with bolus doses available every 1-2 hours • Supplemental oral carbidopa / levodopa is typically administered at night when the infusion stops, but in rare cases, nighttime infusion is necessary **ODT** • Dissolve tablet on top of tongue before swallowing	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
LEVODOPA-CONTAINING COMBINATION PRODUCTS (CONTINUED)				
Levodopa/carbidopa/ entacapone (Stalevo)	Initial: if previously receiving entacapone, dose should be based on previous carbidopa/ levodopa amount. If not, add entacapone separately prior to use of combination product because entacapone increases effect of levodopa and levodopa dose may need reduction, esp. if > 600mg/day MDD: 8 tablets per day or not more than 200/2,000mg carbidopa/ levodopa per day	Tablet: 50/12.5/200mg, 75/18.75/200mg, 100/25/200mg, 125/31.25/200mg, 150/37.5/200mg, 200/50/200mg NOTE: Unlike carbidopa/levodopa products, strengths list levodopa amount first	• Price comparable to separate administration of generic carbidopa/ levodopa + entacapone	N
NON-ERGOTAMINE DOPAMINE AGONISTS				
Pramipexole (Mirapex, Mirapex ER)	Initial (IR tablet): 0.125mg PO TID Initial (ER tablet): 0.375mg PO QD MDD: 4.5mg/day	Tablet: 0.125mg, 0.25mg, 0.5mg, 0.75mg, 1mg, 1.5mg Tablet (ER)*: 0.375mg, 0.75mg, 1.5mg, 2.25mg, 3mg, 3.75mg, 4.5mg	**Non-ergotamine dopamine agonists** • Less effective than carbidopa-levodopa and 3x more likely to induce hallucinations[8] • Adverse effects include orthostasis, N/V, vivid dreams, sleep attacks, impulse control disorders (most common cause)[9] • Typically administered with meals to reduce nausea, but can be taken without meals if tolerated[8] **Pramipexole & Ropinirole** • Require renal dose adjustment **Pramipexole** • Also improves depressive symptoms; consider in patients with both motor and mood symptoms[4,9] **Ropinirole** • XL formulation more effective in reducing Off time[9]	Y/N*
Ropinirole (Requip, Requip XL)	Initial (IR Tablet): 0.25mg PO TID Initial (ER Tablet): 2mg PO QD MDD: 24mg/day	Tablet: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg, 5mg Tablet (ER)*: 2mg, 4mg, 6mg, 8mg, 12mg		Y/N*
Rotigotine (Neupro)	Initial: 2mg/24-hour topically and changed QD (early-stage) or 4mg/24-hour (advanced-stage) MDD: 16mg/day	Transdermal patch: 1mg/24-hour, 2mg/24-hour, 3mg/24-hour, 4mg/24-hour, 6mg/24-hour, 8mg/24-hour		-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
TREATMENTS FOR OFF EPISODES				
Apomorphine (Apokyn, Kynmobi)	Initial (SL): 10mg Q2 hours PRN (NOTE: initial dose should be determined when patient is in Off state and under medical supervision with BP and HR monitoring) Initial (SQ): 2mg as test dose (NOTE: test dose should only be administered under medical supervision). Subsequent dosing is based on response and tolerability. MDD (SL): 5 doses or 150mg/day MDD (SQ): 5 injections or 20mg/day	Solution for injection: 30mg/3ml Sublingual film: 10mg, 15mg, 20mg, 25mg, 30mg	• Dopamine agonist • Dosed as needed for acute intermittent Off episodes • Contraindicated with 5-HT_3 antagonists like ondansetron • Severe nausea / vomiting often occurs w/ use; three days of pretreatment with trimethobenzamide is recommended and can be continued for up to 2 months • Adverse effects are similar to other dopamine agonists • Expensive **Solution for injection** • Limited distribution drug only available through specialty pharmacies • Use lower 0.1mg starting dose if renal impairment • Rotate injection site (abdomen, upper arm/leg) with each use • Restart initial titration if therapy interruption >1 week **Sublingual film** • Commonly causes oral irritation / swelling; if intolerable, discontinue and do not rechallenge • Do not remove from pouch until immediate use planned • Administer whole dose SL; do not cut / chew / swallow	-
Istradefylline (Nourianz)	Initial: 20mg PO QD (40mg QD if smoker and ≥20 cigarettes/ day) MDD: 40mg/day	Tablet: 20mg, 40mg	• Adenosine receptor antagonist • Dosed routinely to prevent Off episodes • May cause or worsen dyskinesias, ICDs, psychosis • Expensive	Y
Levodopa (Inbrija)	Initial: inhale contents of two capsules (84mg total) as needed for Off period MDD: 420mg/day (five doses of 84mg per day)	Dry Powder Inhaler (DPI): 42mg/capsule	• Dopamine precursor • Dosed as needed for acute intermittent Off episodes • Cough is most common adverse effect (up to 60%) • Do not swallow capsules • Expensive	-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MONOAMINE OXIDASE-B (MAO-B) INHIBITORS				
Rasagiline (Azilect)	Initial: 0.5mg PO QD (if receiving levodopa) or 1mg QD (not receiving levodopa) MDD: 1mg/day	Tablet: 0.5mg, 1mg	**MAO-B inhibitors** • Serotonergic drug / food interactions are typically clinically insignificant[20] **Rasagiline, Safinamide** • Expensive	Y
Safinamide (Xadago)	Initial: 50mg PO QD MDD: 100mg/day	Tablet: 50mg, 100mg	**Safinamide** • Only indicated for use in combination with levodopa	Y
Selegiline (Eldepryl, Zelapar)	Initial (Capsule/Tablet): 5mg PO BID Initial (ODT): 1.25mg dissolved on top of tongue QD MDD (Capsule/ODT/ Tablet): Same as initial dosing	Capsule: 5mg Oral Disintegrating Tablet (ODT): 1.25mg Tablet: 5mg	**Selegiline** • Transdermal patches are indicated for depression only. • Do not eat or drink for 5 minutes before or after ODT doses. • Metabolized to amphetamine metabolites. This is of negligible clinical significance, but can cause positive test on urine drug screen.[20]	Y
ANTICHOLINERGICS				
Benztropine (Cogentin)	Initial: 0.5-2mg/day PO divided QHS-QID MDD: 6mg/day	Tablet: 0.5mg, 1mg, 2mg	• Use has fallen out of favor as more effective, better tolerated medications available • Poorly tolerated by geriatric patients • May be considered in young individuals with prominent tremor[4]	Y
Diphenhydramine (Benadryl)	Initial: 25-50mg PO TID-QID MDD: 400mg/day	Capsule: 25mg, 50mg Chewable tablet: 12.5mg Syrup: 12.5mg/5ml Tablet: 25mg, 50mg		Y
Trihexyphenidyl (Artane)	Initial: 1mg/day PO MDD: 15mg/day	Elixir: 0.4mg/ml Tablet: 2mg, 5mg		Y

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
CATECHOL-O-METHYLTRANSFERASE (COMT) INHIBITORS				
Entacapone (Comtan)	Initial: 200mg with each carbidopa/ levodopa dose MDD: 1,600mg/day (8 doses per day)	Tablet: 200mg	**COMT-inhibitors** • Use only in combination with carbidopa/levodopa **Entacapone & tolcapone** • Cause brownish-orange urinary discoloration **Entacapone** • Delayed onset diarrhea can occur, typically 1-3 months after starting **Opicapone** • Reduce dose to 25mg if moderate liver impairment; avoid use if severe impairment • Avoid use if ESRD • Expensive **Tolcapone** • More effective than entacapone, but less commonly used due to required LFT monitoring for hepatotoxicity[9]	Y
Opicapone (Ongentys)	IInitial: 50mg PO QHS MDD: same as initial dosing	Tablet: 25mg, 50mg		Y
Tolcapone (Tasmar)	Initial: 100mg PO TID MDD: 600mg/day	Tablet: 100mg		Y
ATYPICAL ANTIPSYCHOTICS FOR PARKINSON DISEASE PSYCHOSIS				
Clozapine (Clozaril, FazaClo)	Initial: 6.25mg/day PO divided QD-BID MDD: 50mg/day	Orally Disintegrating Tablet (ODT): 12.5mg, 25mg, 100mg, 150mg, 200mg Suspension: 50mg/ml Tablet: 25mg, 50mg, 100mg, 200mg	• Difficult to use in the hospice setting due to requirement for patient / pharmacy / prescriber registration into Risk Evaluation Mitigation Strategy (REMS) that mandates blood monitoring for neutropenia • May also reduce dyskinesia[9]	Y
Pimavanserin (Nuplazid)	Initial: 34mg PO QD unless also receiving a strong CYP3A4 inhibitor, then 17mg QD MDD: 34mg/day	Capsule: 34mg Tablet: 10mg, 17mg	• Limited distribution / specialty medication; not available at all pharmacies • Effect is delayed by several weeks after starting[25] • Expensive	Y
Quetiapine (Seroquel)	Initial: 12.5-25mg PO QHS MDD: 200mg/day	Tablet: 25mg, 50mg, 100mg, 200mg, 300mg, 400mg Tablet (XR)*: 50mg, 150mg, 200mg, 300mg, 400mg	• Less effective than clozapine or pimavanserin, but prescribed first-line by many clinicians due to familiarity, cost, and convenience	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
MISCELLANEOUS				
Amantadine (Symmetrel, Gocovri, Osmolex)	Initial (IR forms, syrup): 100mg PO QD; may increase to BID after at least one week Initial (ER capsule): 137mg QD x1 week, then 274mg QD Initial (ER tablet): 129mg once daily MDD (IR forms, syrup): 400mg/day MDD (ER capsule): 274mg/day MDD (ER tablet): 322mg/day	Capsule: 100mg Capsule (ER): 68.5mg, 137mg Syrup: 50mg/5ml Tablet: 100mg Tablet (ER)*: 129mg, 193mg, 258mg	• NMDAr antagonist • Most useful for levodopa-induced dyskinesia treatment and efficacy is often maintained for long periods[9] • May provide modest reduction in PD motor symptoms[20] • Confusion, livedo reticularis and ankle edema are notable adverse effects • Contents of ER capsules can be sprinkled onto soft food for immediate administration • Requires renal dose adjustment	Y/N*
Carbidopa (Lodosyn)	Initial: 25mg PO with one dose of carbidopa/levodopa (first dose of the day if 10/100mg strength or any dose if other strengths) MDD: 200mg/day	Tablet: 25mg	• Patients generally receive adequate carbidopa from carbidopa/levodopa combination products, so rare to need supplemental carbidopa (~ 75mg/day effectively blocks peripheral dopa decarboxylase)[9,20] • Expensive	Y

References

1. Parkinson Foundation website, accessed online, Sept. 2021 at: https://www.parkinson.org/.
2. Caproni, s. et al. Diagnosis and Differential Diagnosis of Parkinson Disease, *Clin Geriatr Med,* 36 (2020): 13-24.
3. Hanger, HC et al. Cerumen: its fascination and clinical importance: a review, *J Royal Soc Med*, 1992; 85: 346-9.
4. Armstrong, M et al. Diagnosis and Treatment of Parkinson Disease – A Review, *JAMA,* 2020; 323(6): 548-560.
5. Tarsy, D. Motor fluctuations and dyskinesia in Parkinson disease, UpToDate, accessed online Mar. 2019.
6. Kalia, L et al. Parkinson's disease, *Lancet*, 2015; 386(9996): 896-912.
7. Davie, C. A review of Parkinson's disease, *British Medical Bulletin*, 2008; 86(1): 109-27.
8. Ahlskog, JE. Parkinson Disease Treatment in Hospitals and Nursing Facilities: Avoiding Pitfalls, *Mayo Clin Proc,* 2014; 89(7): 997-1003.
9. Connolly, B et al. Pharmacological treatment of Parkinson disease – A review, *JAMA*, 311(16): 1670-83.
10. Papapetropoulos, S et al. Motor fluctuations and dyskinesias in advanced/end-stage Parkinson's disease: a study from a population of brain donors, *J Neural Transm*, 2007; 114: 341-45.
11. Rizek, P et al. An update on the diagnosis and treatment of Parkinson disease, *CMAJ*, 2016; 188(16): 1157-63.
12. Contin, M et al. Pharmacokinetic Optimisation in the Treatment of Parkinson's Disease, *Clin Pharmacokinet*, 1996; 30(6): 463-81.
13. Grimes, D et al. Canadian guideline for Parkinson disease, *CMAJ*, 2019; 191(36): E989-1004.
14. Sherman, S et al. Case Reports Showing a Long-Term Effect of Subanesthetic Ketamine Infusion in Reducing L-DOPA-Induced Dyskinesias, *Case Reports in Neurology*, 2016; 8: 53-8.
15. Moore, H et al. Management of Motor Features in Advanced Parkinson Disease, *Clin Geriatr Med*, 2020; 36: 43-52.
16. Gros, P et al. Overview of Sleep and Circadian Rhythm Disorders in Parkinson Disease, *Clin Geriatr Med*, 202; 36:119-30.
17. Brandt, N. et al. Update on the Management of Parkinson's Disease: Focus on Psychosis, *The Consultant Pharmacist*, 2016; 31(9) Supplement A.
18. American Parkinson Disease Association, Medications To Be Avoided or Used with Caution in Parkinson's Disease, 2018; accessed online Sept. 2019 at: https://www.apdaparkinson.org/wp-content/uploads/2018/05/APDA-Meds_to_Avoid.pdf
19. Holmes, H et al. Soliciting an Herbal Medicine and Supplement Use History at Hospice Admission, *J Pall Med,* 2010; 13(6).
20. Pharmacotherapy Handbook, 12th ed. 2017, McGraw-Hill Education. Pharmacotherapy Quick Guide Chapter 56: Parkinson Disease.
21. Legge, J et al. Gastrointestinal Care of the Parkinson Patient, *Clin Geriatr Med*, 2020; 36: 81-92.
22. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2021.
23. Hauser, R et al. How to Dose Carbidopa and Levodopa Extended-Release Capsules (Rytary), *Clinical Medicine Journal,* ¬2015; 1(2): 34-7.
24. American Parkinson Disease Association website; accessed online Sept. 3rd 2021 at: https://www.apdaparkinson.org/article/medication-rytary/
25. Ramirez-Zamora, A et al. Hospital Management of Parkinson Disease Patients, *Clin Geriatr Med*, 2020; 36: 173-81.

Restless Legs Syndrome

DEFINITION

Restless legs syndrome (RLS), also called Willis-Ekbom disease, is a neurological movement disorder characterized by an irresistibly strong urge to move the legs, occurring during times of inactivity, often interfering with sleep and associated with unpleasant sensations in the legs.[1, 2]

CAUSES

- Primary: abnormal dopamine transmission and/or familial component[1 – 4]
- Secondary: due to associated conditions or medications[1 – 6]
  - » Associated conditions
    - ° Circulatory conditions: venous insufficiency, peripheral vascular disease, iron deficiency
    - ° Neurologic conditions: Parkinson disease, multiple sclerosis, peripheral neuropathy
    - ° Painful conditions: orthopedic problems, arthritis, fibromyalgia, migraine
    - ° Psychologic conditions: ADHD, anxiety, depression, sun-downing
    - ° Renal disease, liver disease
    - ° Respiratory conditions: COPD, pulmonary hypertension, lung transplantation
    - ° Sleep disorders: Periodic limb movements of sleep, insomnia, sleep walking
  - » Medications
    - ° Antidepressants: TCAs, SSRIs, SNRIs (except for desipramine and bupropion)
    - ° Antipsychotics and dopamine-blocking antiemetics (eg, haloperidol, prochlorperazine, metoclopramide)
    - ° Donepezil
    - ° Stimulating substances (eg, caffeine, psychostimulants, theophylline)

HOW TO RECOGNIZE SYMPTOM

- An RLS diagnosis is supported by four symptomatic criteria that cannot be attributed to another medical or behavioral condition.[1, 3]
  - » An urge to move the limbs that is usually associated with uncomfortable and unpleasant sensations
  - » Symptoms that begin or worsen during rest or inactivity
  - » Symptoms exclusively present or worse in the evening or night
  - » Symptoms temporarily relieved by movement
- Patients may report pain and use symptomatic descriptors such as aching, burning, stinging, need to move, cramping, pulling, electric, tension, or itching.[1, 2, 5]
- Signs suggestive of RLS in cognitively impaired patients are evening hyperactivity manifested as foot tapping, pacing, fidgeting, tossing/turning in bed, and rubbing or kneading legs.[4]
- Consequences of untreated RLS include sleep-onset insomnia, nocturnal awakenings, depression, distress, and anxiety.[1, 5, 7, 8]
- RLS is commonly accompanied by periodic limb movements of sleep (PLMS) which are stereotypic, repetitive, periodic movements of the legs that occur during sleep every 20 to 40 seconds and last 10 minutes to several hours.
  - » Since many patients are unaware of these movements, PLMS may only be identified by a bed partner unless it is confirmed during a sleep study.[1 – 3, 5, 7]
  - » PLMS not accompanied by insomnia or excessive daytime sleepiness do not require treatment.

CLINICAL INSIGHTS

- Primary RLS is a lifelong incurable condition and is more common in female and elderly patients.[1, 3, 4]
- Secondary RLS may subside with resolution of precipitating factors; therefore, treat suspected underlying condition(s) prior to initiating drug therapy.[4]
- Screen for RLS in all patients reporting insomnia.
- Drug treatment may not be warranted if RLS symptoms do not interfere with sleep, daytime function, or quality of life for the patient or their bed partner.[8]
- Choice of treatment should be based on symptom severity, patient age and comorbidities, drug side effect profiles and patient preferences.[8] Use the minimum effective dose to minimize daytime sleepiness and other adverse effects.[4]

- Non-pharmacologic therapies may be sufficient for symptom relief in patients with mild or intermittent symptoms.
  - » Avoid aggravating factors such as stress and caffeine/alcohol consumption later in the day.
  - » Non-pharmacologic preventive measures include regular physical activity, adequate sleep, acupuncture, hot baths, leg massage, and use of compression devices/stockings or vibration pads.[1, 3, 4, 7, 8]
- Although iron deficiency (serum ferritin <50mcg/L) is a known cause of RLS, iron supplementation should not be prescribed empirically.[8, 9]
  - » There is insufficient evidence to support the efficacy of oral ferrous sulfate for treating RLS and its adverse effects (eg, GI discomfort, constipation, nausea, reflux, and diarrhea) may limit utility.
  - » While some IV iron formulations may be efficacious, their use may not be appropriate in the hospice population due to burdens of IV placement and monitoring.
- Dopamine agonists (non-ergot-derived) are typically first-line therapy for treating RLS and PLMS, but have side effects requiring careful monitoring, particularly in geriatric patients, including orthostatic hypotension.[1 – 3, 7, 10]
  - » Ergot-derived dopamine agonists (bromocriptine, cabergoline, and pergolide) are not recommended due to serious cardiac risks.[7, 11]
  - » Avoid dopamine agonists in patients with a history of impulsive behavior or psychoses.[2, 4]
  - » Dopamine agonists may be used on a PRN basis for intermittent symptoms.
- Augmentation is a complication of dopaminergic therapy characterized by earlier onset and increased intensity of symptoms, shorter duration of drug action, or spread of symptoms to previously unaffected body parts.[1, 3, 7 – 9]
  - » Risk is highest with higher daily doses and longer duration of therapy (≥6 months) and should be suspected if increasing doses of dopaminergic medications make symptoms worse.
  - » Tramadol therapy has been implicated as a potential cause of augmentation.[8]
  - » Augmentation differs from end-of-dose rebound which can cause worsening of early morning symptoms, but doesn't generally involve spread to arms.
  - » Mild augmentation can be treated by splitting dose between nighttime and earlier in the day.
  - » Severe augmentation can be treated by switching to transdermal rotigotine or a gabapentinoid.[7, 8]
- Gabapentinoids should be considered preferentially in patients with pain, peripheral neuropathy, anxiety, or insomnia.[8]
  - » Gabapentinoids have the advantage of improved sleep and no significant augmentation, but can cause dizziness and daytime sleepiness.[7, 8, 12]
  - » Pregabalin has comparable efficacy for RLS at 12 weeks when compared to pramipexole.[7, 8]
  - » Gabapentin bioavailability is inversely proportional to its dose due to saturable absorption of low-capacity transporters in the small intestine and a non-linear pharmacokinetic profile, reduced from 80% at lower doses (100mg Q8 hours) to 27% at higher doses (1600mg Q8 hours).[10, 13]
  - » Gabapentin enacarbil, a prodrug of gabapentin, is absorbed by high-capacity nutrient transporters throughout the GI tract resulting in non-saturable absorption and linear pharmacokinetics. Since bioavailability remains steady (75%) and dose increases result in proportional drug exposure, gabapentin enacarbil is likely to produce therapeutic effects at doses that are lower than those required for treatment with gabapentin.[12 – 15]
  - » Generic gabapentin has been used successfully prior to the advent of gabapentin enacarbil and may be considered for use in the hospice setting due to the higher cost of the enacarbil formulation and capitated hospice reimbursement.
- Opioids may be an effective option for chronic, refractory RLS, in patients who have failed other therapies.[1 – 5, 8, 9, 16]
- Combination therapy may be necessary if symptoms don't respond to monotherapy.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
DOPAMINE AGONISTS				
Pramipexole (Mirapex) [1 – 4, 6, 8 – 10, 17]	Initial: 0.125mg PO QD, 2 to 3 hours before symptoms occur Titrate by 0.125mg every 4 to 7 days until response CrCl 30-50ml/min: titrate every 14 days MDD: 0.75mg/day	Tablet: 0.125mg, 0.25mg, 0.5mg, 0.75mg, 1mg, 1.5mg Tablet (ER)*: 0.375mg, 0.75mg, 1.5mg, 2.25mg, 3mg, 3.75mg, 4.5mg	**Dopamine Agonists** • For moderate to severe symptoms • Monitor for orthostasis, compulsive behaviors, early morning rebound symptoms, and augmentation • May cause hallucinations, nausea • Do not discontinue abruptly; gradually reduce dose to avoid worsening symptoms **Pramipexole** • To discontinue, gradually reduce dose every 4 to 7 days • CrCl <30ml/min: ER not recommended • Nausea more common with higher doses **Pramipexole & Ropinirole** • Long-acting formulation not well studied in RLS **Ropinirole** • Since most patients require doses ≥2mg, an adequate trial may take 3-4 weeks due to slow titrations **Rotigotine** • May cause peripheral edema • Rotate application sites to minimize application site reactions (do not apply to the same site more than once every 14 days) • To discontinue, gradually reduce dose by 1mg/24hr QOD • Patches >3mg/24hr not approved for RLS	Y/N*
Ropinirole (Requip) [1 – 4, 6, 8 – 10, 17]	Initial: 0.25mg PO QD, 1 to 3 hours before bedtime Titrate by 0.25mg every 2 to 3 days until response MDD: 4mg/day (3mg if ESRD and on hemodialysis)	Tablet: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg, 5mg Tablet (ER)*: 2mg, 4mg, 6mg, 8mg, 12mg		Y/N*
Rotigotine (Neupro) [1 – 3, 7 – 10, 17]	Initial: 1mg TD patch changed QD Titrate by 1mg/24hr at weekly intervals until response MDD: 3mg/day	Transdermal: 1mg/24hr, 2mg/24hr, 3mg/24hr, 4mg/24hr, 6mg/24hr, 8mg/24hr		-

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
GABAPENTINOIDS				
Gabapentin (Neurontin) [1 – 3, 6 – 11, 16, 17]	Initial: 300mg PO QD, 2 hours before bedtime Titrate dose every 1 to 2 weeks until response MDD: 2,400mg/day (see Table 1 for renal dose adjustments)	Capsule: 100mg, 300mg, 400mg Oral solution: 250mg/5ml Tablet: 600mg, 800mg	**Gabapentinoids** • Consider if comorbid neuropathic pain • May cause dizziness, drowsiness, dry mouth, headache, sedation • May cause peripheral edema; use caution in patients with heart failure • Requires renal dose adjustments based on CrCl (see **Table 1**) • Start low and titrate as tolerated (start at lower end of initial dosing range in patients >65 years old) **Gabapentin** • Usual effective dose is 900-2,400mg/day • Divide doses ≥600mg/day as ⅓ daily dose at midday and ⅔ daily dose in PM • 200mg dose may be effective for patients undergoing hemodialysis **Gabapentin enacarbil** • FDA approved for RLS • May discontinue abruptly without tapering if dose ≤600mg/day • Gabapentin enacarbil is not interchangeable with gabapentin due to pharmacokinetic differences • Expensive **Pregabalin** • To discontinue, reduce dose gradually to avoid side effects • Expensive	Y
Gabapentin enacarbil (Horizant) [2 – 4, 7 – 10, 12 – 15, 17, 18]	Initial: 300-600mg PO QD at 5 pm MDD: 1,200mg/day (see Table 1 for renal dose adjustments)	Tablet (ER): 300mg, 600mg		N
Pregabalin (Lyrica) [2, 4, 7 – 10]	Initial: 50mg – 75mg PO QD, given 1 to 3 hours before bedtime Titrate by 75mg/day every 5 to 7 days (max 300mg/day within one week) until response MDD: 450mg/day (see Table 1 for renal dose adjustments)	Capsule: 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg Oral Solution: 20mg/ml Tablet (CR)*: 82.5mg, 165mg, 330mg		Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
OTHER				
Carbidopa/Levodopa (Sinemet, Sinemet CR, Rytary) [1, 2, 4, 6, 8, 10]	Initial dose (25/100mg tablet): 0.5 to 1 tablet PO in the evening, at HS, or upon awakening during the night MDD: 50mg/200mg	Capsule (ER)*: 23.75/95mg Oral Disintegrating Tablet (ODT)*: 10/100mg, 25/100mg, 25/250mg Tablet: 10/100mg, 25/100mg, 25/250mg Tablet (CR): 25/100mg, 50/100mg	• Preferred for intermittent RLS • Quick onset, short duration of action • Augmentation more common with levodopa doses ≥200mg and QD dosing • High protein diets may reduce efficacy • For symptoms that wake patient during the night, use CR tablet before bedtime • Avoid use with MAOIs • Do not discontinue abruptly; gradually reduce dose to avoid worsening symptoms	Y/N*
Clonazepam (Klonopin) [3, 4, 6, 8, 10, 16]	Initial: 0.5mg PO QD, 30 minutes prior to bedtime Titrate by 0.5 to 1mg at weekly intervals MDD: 2mg/day	Oral disintegrating tablet(ODT)*: 0.125mg, 0.25mg, 0.5mg, 1mg, 2mg Tablet: 0.5mg, 1mg, 2mg	• May be useful for intermittent RLS or as an add-on agent for refractory symptoms • Only benzodiazepine studied consistently for RLS • Monitor for carryover sedation due to long half-life • Monitor for nocturnal unsteadiness, drowsiness or cognitive impairment	Y/N*

TABLE 1 – RENAL DOSING RECOMMENDATIONS FOR GABAPENTINOIDS [10]

CREATININE CLEARANCE (CRCL)	GABAPENTIN	GABAPENTIN ENACARBIL	PREGABALIN
30-59 ml/min	200-700mg BID	300mg QD; increase to 600mg QD if needed	75-225mg QD
15-29 ml/min	200-700mg QD	300mg QD	25-150mg QD
15 ml/min	100-300mg QD	-	-
<15 ml/min	Reduce daily dose in proportion based on dose for CrCl 15ml/min (eg, reduce dose by 50% for CrCl 7.5ml/min: 50-150mg QD)	300mg QOD	25-75mg QD

References

1. Bayard, M. et al. Restless leg syndrome. In: Ebell MH, ed. Essential Evidence Plus & AHFS DI Essentials. Hoboken, NJ: Wiley Subscription Services; 2018.
2. Clinical resource, Treatment of restless legs syndrome. Pharmacist Letter/ Prescriber's Letter. April 2017.
3. Dopp, J. et al. Sleep-wake disorders. In: DiPiro J; Talbert R; et.al. Pharmacotherapy: A Pathophysiologic Approach, 10e. New York, NY: McGraw-Hill Education; 2017.
4. Watenpaugh, D. et al. Restless legs syndrome. In: Domino FJ, ed. The 5-minute clinical consult. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.
5. Ondo, W. et al. Clinical Features and diagnosis of restless legs syndrome and periodic limb movement disorder in adults. UpToDate. Waltham, MA: UpToDate Inc.; 2018.
6. Chai, E. et al. End-Stage Renal Disease. In: Geriatric Palliative Care: A practical guide for clinicians. New York, NY: Oxford University Press; 2014.
7. Salminen, A. et al. Restless Legs Syndrome and Other Movement Disorders of Sleep - Treatment Update. Current treatment options in neurology. 2018;20(55):1-12.
8. Silber, M. et al. Treatment of restless legs syndrome and periodic limb movement disorder in adults. UpToDate. Waltham, MA: UpToDate Inc.; 2018.
9. Winkelman, J. et al. Practice guideline summary: Treatment of restless legs syndrome in adults. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2016; 87(24):2585-2593.
10. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2018.
11. Aurora, R. et al. The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder in Adults - An Update for 2012: Practice Parameters with an Evidence-Based Systematic Review and Meta-Analyses. SLEEP. 2012;35(8):1039-1062.
12. Burke, R. et al. Review of the Treatment of Restless Legs Syndrome: Focus on Gabapentin Enacarbil. Journal of Central Nervous System Disease. 2012;4:147-156.
13. Bockbrader, H. et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clinical Pharmacokinetics.2010;49(10):661-669.
14. Sivam, S. et al. Role of gabapentin enacarbil XR in restless legs syndrome. Therapeutics and Clinical Risk Management. 2012;8:201-208.
15. Gabapentin enacarbil (Horizant). National Drug Monograph. VA Pharmacy Benefits Management Services. March 2012.
16. Melzack, R. et al. Handbook of Pain Management. Edinburgh: Churchill Livingstone; 2003.
17. Drug Facts & Comparisons. Facts & Comparisons. St Louis, MO: Wolters Kluwer Health, Inc.; 2019.
18. Winkelmann, J. et al. Treatment of restless legs syndrome: Evidence-based review and implications for clinical practice (Revised 2017). Movement Disorders. 2018; 33(7):1077-1091.

Thyroid Disorders

DEFINITION

Hyperthyroidism, also called thyrotoxicosis, is a disorder of an overactive thyroid gland resulting from increased synthesis and/or secretion of thyroid hormones.

Hypothyroidism is a disorder of an underactive thyroid gland resulting from decreased synthesis and/or secretion of thyroid hormones.

CAUSES

HYPERTHYROIDISM [1-4]

- Iodine excess
- Medical Conditions
  - » Graves' Disease (most common cause), also called autoimmune thyroiditis
  - » Toxic multinodular goiter (Plummer's disease)
  - » Thyroiditis
  - » Tumors: Toxic adenoma, Pituitary tumor (TSH-secreting)
- Medications / Diagnostic agents
  - » Antineoplastics including aldesleukin, interferon-alfa, checkpoint inhibitor immunotherapy (eg, ipilimumab, pembrolizumab)
  - » Amiodarone (less commonly than hypothyroidism)
  - » Iodinated contrast media
  - » Lithium (less commonly than hypothyroidism)
  - » Levothyroxine (therapeutic excess)

HYPOTHYROIDISM [5-9]

- Iodine deficiency or excess
- Medical Conditions:
  - » Hashimoto's Thyroiditis (most common cause)
  - » Pituitary insufficiency (secondary hypothyroidism)
  - » Hypothalamic dysfunction
  - » Infiltrative thyroid disease (may result from generalized diseases including amyloidosis, sarcoidosis, scleroderma, cystinosis, hereditary hemochromatosis)
- Medications
  - » Antineoplastics including aldesleukin, interferon-alfa, tyrosine kinase inhibitors (sunitinib most common), and checkpoint inhibitor immunotherapy (eg, ipilimumab, pembrolizumab)
  - » Lithium
  - » Amiodarone
  - » Hyperthyroidism treatments: methimazole, propylthiouracil
  - » Tyrosine kinase inhibitors (eg, sunitinib)
- Radiation exposure (radioiodine or external radiation, especially neck irradiation)
- Thyroidectomy (up to 49% of patients)

HOW TO RECOGNIZE

- Thyroid dysfunction can lead to signs and symptoms that affect multiple organ systems and bodily functions. (**Table 1**)
- Diagnosis of hyper – and hypothyroidism is confirmed through laboratory measurement of serum TSH levels which is not commonly performed in the hospice setting. (**Table 2**)
- An enlarged thyroid gland, or goiter, may be present in either condition.

TABLE 1 – COMMON SIGNS AND SYMPTOMS OF THYROID DISORDERS

HYPOthyroidism [5-8]		HYPERthyroidism [1, 2, 4, 7, 10]
Bradycardia Facial puffiness Periorbital swelling	**Circulatory**	Tachycardia Palpitations
Constipation	**GI**	Diarrhea
Muscle cramps Myalgia Stiffness	**Neuromuscular**	Tremor
Fatigue Memory impairment Difficulty concentrating Depression Cold intolerance Slow, hoarse speech	**CNS**	Fatigue Anxiety Insomnia Psychosis Hyperactivity Heat intolerance Rapid speech
Weight gain	**Endocrine/ Metabolic**	Weight loss (despite increased appetite)
Cold or dry skin Coarse skin and hair	**Skin / Hair**	Warm, smooth, moist skin Unusually fine hair Diaphoresis

TABLE 2 – THYROID CONDITIONS DIFFERENTIATED BY THYROID FUNCTION TEST RESULTS[7]

	T_4 (TOTAL)	T_4 (FREE)	T_3 (TOTAL)	TSH
Normal	4.5-10.9mcg/dL	0.8-2.7ng/dL	60-181ng/dL	0.5-4.7mIU/L
Hyperthyroid	↑↑	↑↑	↑↑↑	↓↓
Hypothyroid	↓↓	↓↓	↓	↑↑

HYPERTHYROIDISM

- Elderly patients may present with non-classical signs and symptoms that mimic depression or dementia, making diagnosis challenging[2, 4]
- Patients with subacute thyroiditis, likely the result of a viral infection, may complain of severe pain in the thyroid region that extends to the ear on the affected side.[7]

HYPOTHYROIDISM

- Many signs and symptoms of hypothyroidism are non-specific, making diagnosis difficult in the absence of laboratory confirmation.

CLINICAL INSIGHTS

HYPERTHYROIDISM

- The goal of therapy is to correct the hypermetabolic state while limiting side effects and preventing hypothyroidism[1, 2, 4]
- Primary pharmacologic treatment consists of one of two antithyroid drugs (thionamides), methimazole or propylthiouracil.
  - » If switching from one drug to another, a 1:20 (methimazole : propylthiouracil) ratio is recommended.[11]
- Beta-blockers can be used as adjuvants to relieve adrenergic symptoms (eg, tremor, palpitations, tachycardia, heat intolerance, nervousness)[1–4]
  - » Non-selective beta-blockers (eg, propranolol) are preferred because they have a more direct effect on hypermetabolism[4]
- If remission does not occur with initial antithyroid drug therapy, alternate treatments include radioactive ablation (usually with radioactive iodide, or ^{131}I) of the thyroid or thyroidectomy.[7] Permanent hypothyroidism and subsequent treatment is almost inevitable following these interventions.
- Permanent remission rates are dependent on disease severity and could influence decisions to continue or deprescribe antithyroid drugs.
  - » Approximately 20-30% of patients achieve remission with treatment; rates may be as high as 75% in patients with mild disease.[12]
  - » Longer durations of therapy have been associated with improved remission rates.
  - » Remission is unlikely in severe cases of hyperthyroidism.
- Deprescribing thionamides in hospice patients should be considered on a case-by-case basis.
  - » Typical duration of thionamide treatment is 12 to 18 months, so deprescribing may be evaluated following at least 12 months of treatment, particularly in patients with mild hyperthyroidism.
  - » Abrupt discontinuation can worsen hyperthyroid symptoms and may (rarely) lead to thyroid storm, a life-threatening medical emergency with a high symptomatic burden.[1–3, 7] Therefore, if deprescribing is planned, gradual tapering is recommended.
- Antithyroid drugs are not typically included in the hospice plan of care, but hospices should provide coverage if hyperthyroidism is caused or exacerbated by treatment of a condition that is related or contributing to the terminal diagnosis or prognosis.

HYPOTHYROIDISM

- Hypothyroidism is more common in older adults (> 60 years), especially women [5, 8]
- Most patients with hypothyroidism will require lifelong treatment with levothyroxine (T_4) [8]
  - » There is insufficient evidence to support the use of desiccated thyroid (eg, Thyroid USP, Armour Thyroid) or T_3 (liothyronine)/T_4 combination therapy. [8, 11, 13]
  - » A 3-month trial of combination therapy with T_3/T_4 may be considered when symptoms of hypothyroidism persist despite normal TSH levels with monotherapy, but the added replacement should be discontinued if no observable benefit after the trial. [13]
  - » Methods for converting from desiccated thyroid and T_3/T_4 to T_4 monotherapy have been suggested. (**Table 3**)
- Older patients and patients with coronary artery disease require lower initial dosing, as higher starting doses may precipitate acute coronary syndrome or arrhythmias. [8]
- There is considerable debate on whether brand name and generic levothyroxine preparations are bioequivalent; as a result patients should be started and maintained on either brand name or generic preparations and not switched between the two. [8]
- It is generally recommended that levothyroxine doses are administered 30-60 minutes before breakfast (absorption is optimized on an empty stomach); ultimately, adherence and consistency are most important and doses can be given later in the day, 3 to 4 hours after the evening meal. [11]
- We recommend continued treatment of hypothyroidism in hospice patients as long as oral medications are tolerated.
  - » Continued treatment can aid in palliating distressing symptoms of hypothyroidism and preserve quality of life. [14]
  - » Premature discontinuation of these medications can result in clinically significant worsening of symptoms, especially in patients with a longer prognosis and those on higher doses of thyroid replacement medications.
- Thyroid replacement should be covered by hospice when hypothyroidism is related to head/neck or thyroid cancer, cancer treatment, or treatment of a terminal condition (eg, amiodarone use in a patient with terminal cardiovascular disease), terminal diagnosis of protein calorie malnutrition, or any other scenario where hypothyroid treatment is deemed to be related.

TABLE 3 – THYROID REPLACEMENT CONVERSIONS [15]

FROM	TO	SUGGESTED METHOD
Desiccated thyroid (eg, Thyroid USP, Armour Thyroid)	T_4 (levothyroxine)	1 grain (60mg) : 100mcg (desiccated thyroid : T_4) See Appendix: "Thyroid Hormone Replacement Equivalence (Medication Conversions)"
Combination T_3/T_4	T_4 (levothyroxine)	(T_4 dose) + (4 x T_3 dose) = new T_4 dose

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
ANTITHYROID MEDICATIONS (THIONAMIDES)				
Methimazole[2, 7, 11] (Tapazole)	Initial: 10-60mg PO QD Usual maintenance dose is 5-15mg QD MDD: 120mg/day	Tablet: 5mg, 10mg	• Typically the drug of choice • Dosing varies depending on disease etiology, severity • Usually dosed QD, but can be divided BID if >30mg/day • Rectal administration has been reported in thyrotoxic crisis	Y
Propylthiouracil[2, 7, 11] (Propacil)	Initial: 50-150mg PO Q8H MDD: 1,200mg/day	Tablet: 50mg	• Drug of choice for thyroid storm • High risk of causing severe liver injury/liver failure • Reserved for patients who can't tolerate methimazole • Administer consistently, with meals or without meals, and give doses at the same time each day	Y
ADJUVANT HYPERTHYROIDISM TREATMENTS				
Propranolol[1–4, 7, 11] (Inderal)	Initial: 10mg PO BID-TID MDD: 160mg/day	Capsule (ER)*: 60mg, 80mg, 120mg, 160mg Tablet: 10mg, 20mg, 40mg, 60mg, 80mg	• Off-label use as adjunct treatment for adrenergic symptoms of hyperthyroidism (eg, palpitations, anxiety, tremor, heat-intolerance) • Abrupt withdrawal may exacerbate hyperthyroid symptoms • Take IR tablets on an empty stomach • Doses as high as 480mg/day may be required in severe cases	Y/N*

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
THYROID HORMONE REPLACEMENT				
Levothyroxine[8, 11] (Euthyrox, Levoxyl, Synthroid, Tirosint, Unithroid)	Initial: 1.6mcg/kg/day >50 years: 25-50mcg PO QD history of CAD: 12.5-50mcg PO QD MDD: 300mcg/day	Capsule (Tirosint)*: 13mcg, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 137mcg, 150mcg, 175mcg, 200mcg Oral Solution (Tirosint): 13mcg/ml, 25mcg/ml, 50mcg/ml, 75mcg/ml, 88mcg/ml, 100mcg/ml, 112mcg/ml, 125mcg/ml, 137mcg/ml, 150mcg/ml, 175mcg/ml, 200mcg/ml Solution for injection: 100mcg, 200mcg, 500mcg Tablet: 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 137mcg, 150mcg, 175mcg, 200mcg, 300mcg	• Synthetic T_4 • Administer on an empty stomach • Do not administer within 4 hours of calcium- or iron- containing products, bile acid sequestrants (eg, cholestyramine) • Consider dose reduction if signs/ symptoms of hyperthyroidism • **NG tube:** bioavailability reduced if administered with enteral nutrition; consider small dose increase (eg, 25mcg) • IV/IM formulation typically reserved for treating myxedema coma • Brand name formulations are expensive	Y/N*
Liothyronine[8, 11] (Cytomel)	Initial: 25mcg PO QD Cardiovascular disease: 5mcg PO QD MDD: 75mcg/day	Solution for injection: 10mcg/ml Tablet: 5mcg, 25mcg, 50mcg	• Synthetic T_3 • Should not be used alone for long-term thyroid hormone replacement • T_3/T_4 combination therapy may be considered if symptomatic despite normal TSH • Use with caution in patients with cardiovascular disease and monitor for signs/symptoms of angina	Y

References

1. Kravets I. Hyperthyroidism: Diagnosis and Treatment. American Family Physician. 2016:93(5).
2. Hershman J. Hyperthyroidism. Merck Manuals: Professional Edition. April 2018.
3. Ross DS. Patient education: Hyperthyroidism. UpToDate. Accessed April 2019
4. "Hypothyroidism" National Endocrine and Metabolic Diseases Information Service. NIH publication No 13-6180. March 2013
5. Hershman J. Hypothyroidism. Merck Manuals: Professional Edition. April 2018.
6. Kumar V, et al. Robbins and Cotran Pathologic Basis of Disease. 7th ed., Elsevier Saunders, 2005.
7. DiPiro JT. Pharmacotherapy: a Pathophysiologic Approach. Pg1369-1390. McGraw-Hill, 2005.
8. Reid J, et al. Hyperthyroidism: Diagnosis and Treatment. American Family Physician 2005. 72:623-630.
9. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2018.
10. Gaitonde D, et al. Hypothyroidism: An Update. American Family Physician. 2012; 86(3):244-251.
11. Joven MH. Should the treatment of hypothyroidism be withdrawn in hospice care? Journal of Pain & Symptom Management. 2016:52(3):e3-e4.
12. Ross DS, et al. Treatment of primary hypothyroidism in adults. UptoDate. Accessed December 6 2019.
13. Ross DS. Disorders that cause hypothyroidism. UptoDate. Accessed December 5, 2019.
14. Cooper DS. Antithyroid Drugs. New England Journal of Medicine. 2005;352(9):905.
15. Wiersinga WM, et al. 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. European Thyroid Journal. 2012;1(2):55-71.

OnePoint®
PATIENT CARE

What one can do.®

Drug Monographs

ADDITIONAL CONSIDERATIONS FOR FENTANYL PRESCRIBING

- Transdermal Fentanyl
  - » Conversions to or from transdermal fentanyl
    - ° The time needed for transdermal fentanyl to provide adequate analgesia after application of the first patch needs to be appreciated when converting to fentanyl to avoid worsening of pain control and perceived fentanyl failure (**Table 1**)
    - ° Appreciation of the residual fentanyl depot after patch removal is important to avoid CNS depression when converting from fentanyl patches to other opioids[1] (**Table 2**)
    - ° Converting from another opioid to transdermal fentanyl
      - › Patients will likely need pain coverage for the first 12 hours after the fentanyl patch is applied. This is typically done by either[1]:
        - · Administering one final dose of a long-acting opioid tablet like extended-release morphine or oxycodone at same time the patch is applied.
        - · Administering 3 doses of short-acting opioid, scheduled every 4 hours with the first dose to be administered at the same time the patch is applied.

TABLE 1[2] – TIME TO ANALGESIC EFFECT OF TRANSDERMAL FENTANYL PATCH AFTER APPLICATION

Time (Hours)	12	36	72 to 144
Analgesic Effect	Minimal	Maximal	Steady State

    - ° Once the mathematical calculations are made the dose is rounded up or down to use available patch strengths
      - › Be aware that 37.5mcg/hr, 62.5mcg/hr and 87.5mcg/hr patches are commercially available but are extremely expensive
      - › It is more cost effective to use a 12.5mcg patch with another patch to dose the "middle" range between 25mcg/hr and 50mcg/hr, etc.
  - » Converting from transdermal fentanyl to another opioid
    - ° To avoid CNS depression, account for the residual amount of fentanyl in the subcutaneous tissue when converting from transdermal fentanyl to another opioid. One method to do so is:[1]
      - › Use only short-acting rescue opioid on an as-needed basis for 12 hours after patch removal.
      - › After 12 hours, commence with replacement long-acting opioid at 50% of the calculated dose for a single dose.
      - › After 24 hours, titrate replacement long-acting opioid to 100% of calculated dose.

TABLE 2[3,4] – FENTANYL BLOOD LEVEL REMAINING AFTER REMOVAL OF FINAL FENTANYL PATCH

Time (Hours)	20 to 27	40 to 54	60 to 81	80 to 108
% Of Previous Fentanyl Level Remaining	50%	25%	12.5%	6.25%

  - » Changing and titrating transdermal fentanyl
    - ° Dose titration should not occur more often than 3 days after the initial patch is applied, or every 6 days thereafter
    - ° Fentanyl patches are changed (new one applied, old one discarded) every 72 hours
    - ° Rarely, patients may require every 48-hour administration,[4] (though some references cite a rate of 20%1) but this should be reserved only for patients with documented end-of-dose failure on the third patch cycle day.
    - ° Before decreasing the application interval to 48 hours consider increasing the dose to the next patch strength
    - ° Poor adhesion of fentanyl patches has been cited as a possible reason for end of dose failure[11] (see below for strategies to improve adhesion if this is suspected)
  - » Troubleshooting patch adhesion issues

- Excessive sweating, application site, temperature, blood flow, body fat and skin integrity can affect patch adhesion [7]
- Patches may be taped in place with first-aid tape. If this fails, adhesive dressings like Bioclusive or Tegaderm may be applied over the patch. [5] No other tapes or dressings should be used. [5]
- Anecdotally, rotating from one manufacturer's patch to another can lead to improved adhesion [8]

» Exposure of the patch application area to high temperatures while wearing transdermal fentanyl patches can cause increased delivery of fentanyl and possible opioid overdose [3]

- Do not wear patch in hot tubs, Jacuzzis, saunas, etc. [5]
- Do not expose to heat sources like electric blankets, heating pads, tanning beds, etc. [5]

» Febrile patients or patients with elevated body temperature due to strenuous exertion are transiently at risk for increased exposure. [3, 6] We recommend additional monitoring rather than dose reduction during these circumstances

» Use in older adults and cachectic patients

- Historical anecdotes have suggested transdermal fentanyl to be less effective in cachectic patients. However, the current package insert for Duragesic discusses cachexia only once, stating "life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they have altered pharmacokinetics or clearance compared to younger, healthier patients", which would suggest and increased, rather than decreased effect in cachectic patients. [3]
- To date, there are two conflicting small scientific studies regarding the use of transdermal fentanyl in cachectic patients [9, 10]
  - Heiskanen et al. found reduced plasma fentanyl concentrations after transdermal fentanyl use in cachectic cancer patients compared to normal weight cancer patients. [9] They attributed this observation to be due to cachexia-associated chronic inflammation and hypercatabolism, resulting in poor absorption of fentanyl through cachectic skin. They also stated subcutaneous adipose tissue does not affect transdermal fentanyl absorption.
  - More recently, Suno et al. found increased, rather than decreased fentanyl levels to be associated with cachexia. [10] Cachexia severity positively correlated with fentanyl levels. They attributed the increased levels in cachectic patients to be due to increased inflammatory cytokines causing a decrease in the expression of CYP3A4, the primary metabolizing enzyme responsible for the conversion of fentanyl to norfentanyl.
- Despite the conflicting evidence above, if converting from transdermal fentanyl to another opioid due to a lack transdermal fentanyl efficacy despite adequate titration, use the last effective patch strength, rather than the current patch strength as the starting point for opioid conversions to minimize the risk of opioid overdose.
- A study examining the percent of fentanyl absorbed from patch dosage forms found that patients > 75 years old absorbed 50% of the fentanyl contained in the patch, wheras those <65 years old absorbed 66% [14]

• Transmucosal Immediate Release Fentanyl (TIRF)

» Transmucusal fentanyl preparations are not interchangeable and a lack of comparative studies between dosage forms prevents clinical recommenations from being made regarding the superiority/inferiority of one product over another. [13]

» Advantages:

- Compared to other opioids, TIRF products are reported to have a more rapid onset of 5 to 15 minutes, which can reduce the amount of time patients suffer with pain [4]

- Disadvantages:
  - Because of the risks for misuse, abuse, addiction, and overdose associated with TIRF use, the patient, prescriber, distributer and dispensing pharmacy are required to register in the TIRF-Risk Evaluation and Mitigation Strategy (REMS) program. More information on TIRF-REMS can be found at: http://www.TIRFREMSAccess.com.
  - TIRF products are expensive, often cost-prohibitively in light of limited hospice reimbursement. As such, prior authorization is typically required by hospice organizations.
  - Some TIRF products' labeling limits how often doses can be repeated (eg, after 2 doses of Fentora during a breakthrough episode, must wait 4 hours before treating another episode)[4]
  - Incomplete consumption of TIRF dosages make determining the minimally effective breakthrough dose problematic
  - Compromised oral mucosa may enhance the absorption of transmucosal fentanyl products[13]
- There is limited information available to support opioid conversions involving TIRF
  - Recommendations for converting between TIRF dosage forms are summarized in Table 3.[4]

TABLE 3[4] – CONVERTING BETWEEN TRANSMUCOSAL IMMEDIATE RELEASE FENTNAYL (TIRF) DOSAGE FORMS

		STARTING WITH:				
		Actiq Buccal Lozenge	Fentora Buccal Tablet	Subsys Sublingual Solution	Abstral Sublingual Tablet	Lazanda Nasal Solution
CONVERTING TO:	Actiq Buccal Lozenge		Start at 200mcg	Start at 200mcg	Start at 200mcg	Start at 200mcg
	Fentora Buccal Tablet	If 200-400mcg lozenge, start at 100mcg If 600-800mcg, start at 200mcg If 1,200-1,600mcg lozenge, start at 400mcg		Start at 100mcg	Start at 100mcg	Start at 100mcg
	Subsys Sublingual Solution	If 200-400mcg lozenge, start at 100mcg If 600-800mcg, start at 200mcg If 1,200-1,600mcg lozenge, start at 400mcg	Start at 100mcg		Start at 100mcg	Start at 100mcg
	Abstral Sublingual Tablet	Start at 100mcg	Start at 100mcg	Start at 100mcg		Start at 100mcg
	Lazanda Nasal Solution	Start at 100mcg	Start at 100mcg	Start at 100mcg	Start at 100mcg	

- A published conversion states that 200mcg Actiq is approximately equal to 6 to 12mg of oral morphine.[12] This conversion can be extrapolated to other TIRF dosage forms if their differences in bioavailability are accounted for (**Table 4**).
- Patients transitioning from another opioid to TIRF should start at the initial dose recommended in the product labeling, without regard to their previous opioid dose.

TABLE 4[4, 12] – CONVERTING FROM TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) DOSAGE FORMS TO ORAL MORPHINE EQUIVALENTS (OME)

			STARTING WITH:				
			Published Conversion†	Extrapolations Based On Published Conversion and Bioavailability Differences			
			Actiq Buccal Lozenge	Fentora Buccal Tablet	Subsys Sublingual Solution	Abstral Sublingual Tablet	Lazanda Nasal Solution
		Bioavailability	50%	65%	76%	54%	60%
		Approximate Actiq Equivalent Based On Bioavailability Differences	200	260	304	216	240
CONVERTING TO:	Oral Morphine Equivalents (OME) (mg)	Lower Estimate	6	8	9	6	7
		Upper Estimate	12	16	18	13	14

† Actiq to OME conversion based on conversion published in Medscape article "Difficult-to-dose Opioids and the Risk Evaluation Mitigation Strategy, accessed online June 2017 at: http://www.medscape.com/viewarticle/723243_print. All other conversions are based on relative differences in bioavailability. This table is intended only as a guide and only for conversion from a buccal, sublingual or nasal fentanyl preparation to OME for purpose of converting to morphine or another opioid. It should not be used to convert from one buccal, sublingual or nasal fentanyl preparation to another. Values are rounded to the nearest whole number.

References

1. McPherson, ML, Demystifying Opioid Conversion Calculations – A Guide for Effective Dosing, American Society of Health-System Pharmacists, 2010.
2. Muijsers, R. et al. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control, Drugs, 2001;61(15):2289-307.
3. Duragesic prescribing information, Janssen Pharmaceuticals, Inc., accessed online at: https://www.janssenmd.com/pdf/duragesic/duragesic_pi.pdf, last updated March 2017.
4. Lexicomp, Fentanyl monograph.
5. Medication Guide – Fentanyl Transdermal System, CII, Mallinckrodt Pharmaceuticals, Revised October 2014.
6. Fentanyl Transdermal, Facts & Comparisons eAnswers, accessed online May 2017.
7. Raj Bista, S. et al. Validation of a Fentanyl Transdermal Adhesion Scoring Tool for Use in Clinical Practice, J of Pain and Symptom Management, 2015;49(5):934.
8. Authors' experience
9. Heiskanen, T. et al. Transdermal fentanyl in cachectic cancer patients, Pain, 2009;144:218-22.
10. Suno, M. et al. Refractory cachexia is associated with increased plasma concentrations of fentanyl in cancer patients, Therapeutics & Clin Risk Management, 2015;11:751-7.
11. Arnet, I. et al. Poor adhesion of fentanyl transdermal patches may mimic end-of-dosage failure after 48 hours and prompt early patch replacement in hospitalized cancer patients, J of Pain Research, 2016; 9:993-9.
12. Medscape article "Difficult-to-dose Opioids and the Risk Evaluation Mitigation Strategy, accessed online June 2017 at: http://www.medscape.com/viewarticle/723243_print.
13. Twycross, Wilcock, Howard, ed Palliative Care Formulary, Fifth Edition; 2014; 413-20.
14. Solassol, I. et al. Inter- and intra-individual variability in transdermal fentanyl absorption in cancer pain patients, Oncology Reports, 2005;14(4):1029-36.

ADDITIONAL CONSIDERATIONS FOR METHADONE PRESCRIBING

Methadone is a highly complex synthetic opioid used for the treatment of pain. While it is substantially less expensive than other long-acting opioid formulations cost should not be the sole reason to use it.

- Patient-specific factors should be considered when evaluating patients as candidates for methadone treatment of chronic pain [1, 15]
  - » Characteristics weighing in favor of methadone use:
    - ° Pain refractory to other opioids
    - ° Neuropathic component to pain
    - ° Dysphagia / inability to swallow extended-release dosage forms
    - ° Intolerable adverse effects with other opioids
    - ° Significant renal impairment
    - ° True opioid allergy (rare)
  - » Characteristics weighing against methadone use:
    - ° Limited prognosis / inadequate time to complete conversion process
    - ° Unstable or rapidly escalating pain
    - ° Unpredictable or unreliable medication adherence
    - ° Lives alone / poor cognitive function
    - ° History of arrhythmia or use of additional QTc interval prolonging medications
    - ° Poorly controlled sleep apnea

RISK

- Methadone is involved in a disproportionately high number of opioid overdose cases. Appreciation of methadone's unique pharmacokinetic and pharmacodynamic properties is essential for safe use. [11 – 12]
- Evidence shows that the period shortly following methadone initiation appears to be associated with increased risk of overdose and other adverse effects [11]
- Despite the associated risks, methadone use may confer unique benefits including: [13 – 16]
  - » As a synthetic opioid without active metabolites, it will not cross-react in patients with true opioid allergy and is less likely to cause opioid-induced neurotoxicity [15, 46]
  - » Reduced opioid tolerance and hyperalgesia (via NMDA receptor blocking)
    - ° Once patients are receiving a stable dose of methadone, large dose adjustments are often not needed unless the underlying source of pain worsens [17]
  - » Increased efficacy in treating neuropathic pain (via NMDA receptor blocking and norepinephrine reuptake inhibition)
  - » Ease of administration in patients with dysphagia because the tablets can be crushed and an oral solution is available
  - » Less desirable to patients or others looking to abuse or sell opioids illegally

PROPERTIES

- Pharmacokinetics of methadone
  - » Methadone exhibits non-linear kinetics. There is no fixed conversion ratio between methadone and other opioids because methadone becomes more potent with higher doses. [1]
  - » Absorption
    - ° Rapidly and well-absorbed by nearly all routes (but not transdermally) [16, 18]
  - » Distribution
    - ° Highly protein bound to α1-acid glycoprotein [19 – 21]
      - › Compared to drugs that bind to albumin, there is lower likelihood of clinically relevant drug interactions due to carrier protein competition / displacement
      - › α1-acid glycoprotein concentrations can increase due to a number of causes, including infections, cancer, burns, obesity, inflammatory diseases and medications. The resulting decrease in unbound "free" methadone can potentially result in increased pain / need for higher doses.
    - ° Large volume of distribution
      - › With initial dosing, most methadone is rapidly stored in bodily tissues, mostly the liver, kidneys and lungs [22]

- After steady state is reached, there is an equilibrium between tissue storage and re-distribution into systemic circulation. This equilibrium is in part maintained by P-glycoprotein pumps, which function variably due to inter-individual genetic differences.

» Metabolism

- Hepatically by CYP450 2B6 (primary), 3A4 and 2D614[23 – 24]
  - Long and wide-ranging half-life of approximately 1-day, but can be up to 5 days or more in some patients. Typical half-life is 15 – 60 hours (4 – 5 half-lives are needed to reach steady state)[11]
    - Because of methadone's long half-life, if naloxone is used to reverse opioid overdose, multiple doses are typically needed to sustain the opioid blocking effect
    - Variability in half-life is due to Interindividual genetic differences in CYP450 enzyme subfamily phenotype (2D6, 2B6) and gene expression (3A4)[22, 25]
- Caution should be exercised in patients with hepatic impairment, but some clinical evidence suggests no dose reduction may be needed (potentially due to a reduced ability of the failing liver to store and release methadone)[19, 26]

» Elimination

- Renally and fecally eliminated[14]
  - In patients with renal impairment, fecal excretion increases to compensate[14]
- Methadone is considered a safe opioid in patients with renal impairment, but lower initial doses can be considered for patients with end-stage renal disease[17]

• Drug interactions between methadone and other drugs can result in patient harm[27]

» Pharmacokinetic interactions

- Induction of methadone metabolism (methadone levels go down)
  - Possible consequence: loss of pain control
  - Common strong CYP450 enzyme inducers such as: rifampin, enzyme-inducing antiepileptic drugs (eg, phenytoin, phenobarbital, and carbamazepine)
  - Expected time to interaction: 1 – 2 weeks[31]
  - Recommended intervention: no empiric methadone dose increase; monitor pain control, particularly during the expected time period above and titrate methadone if needed at that time.
- Inhibition of methadone metabolism (methadone levels go up)
  - Possible consequence: increased side effects such as CNS depression, death
  - Common strong CYP450 inhibitors: azole-type antifungals (eg, fluconazole, ketoconazole), clarithromycin, protease inhibitors (eg, ritonavir, indinavir)
  - Expected time to interaction: 1 – 2 days[31]
  - Recommended intervention: avoid concomitant use of strong CYP450 inhibitors in patients receiving methadone. If use is unavoidable, an empiric methadone dose reduction of 25% is recommended to avoid CNS depression secondary to increased methadone levels.[15]

» Pharmacodynamic interactions

- Additive QTc interval prolongation with other QTc interval prolonging medications (See appendix for list) potentially resulting in ventricular arrythmia
  - Generally, attempts should be made to minimize the total number of medications that prolong the QTc interval
    - For example, if a patient receiving methadone requires antibiotic therapy for the treatment of a respiratory infection, avoid fluoroquinolones and macrolides in favor of penicllins and tetracyclines.
- Central nervous system (CNS) depression
  - The risk of CNS depression increases with the total number of CNS depressing drugs being taken

› Avoid unnecessary use of CNS depressing medications, but recognize that in the hospice setting it is common for opioids and benzodiazepines to be co-prescribed to provide relief of distressing symptoms.

° Serotonin syndrome is a group of symptoms that have the potential to occur when a patient takes one or more medications that causes excessive serotonin activity[47]

› Serotonin syndrome is rare and avoidance should typically not be heavily weighted when evaluating the risks and benefits of methadone use[8]

› Generally, minimize the total number of medications that increase the risk of serotonin syndrome.

· Drugs that have the potential to cause or contribute to Serotonin syndrome include serotonergic antidepressants (eg, SSRIs, SNRIs, TCAs, mirtazapine, etc.), triptans, dextromethorphan, metoclopramide, ondansetron, chlorpheniramine, tramadol and others.

› Mild symptoms may include agitation, restlessness, confusion, shivering, diarrhea, headache, and muscle rigidity. These symptoms can resolve as rapidly as one day after stopping the offending drug(s).

› Severe symptoms can be life-threatening and may include high fever, seizures, arrhythmia and loss of consciousness.

› Treatment of severe serotonin syndrome is individualized and may include cyproheptadine (a serotonin blocking antihistamine), benzodiazepines for agitation/seizure/rigidity, and other supportive care.

- Side effects

» The peak respiratory depressant effect of methadone occurs after and lasts longer than the peak analgesic effect[18]

° Methadone should be limited to scheduled use for the management of chronic pain[15, 28]

» Side effects that would be expected with other opioids, such as constipation and sedation, should be expected with methadone as well[28]

° Case reports have been published where methadone caused less constipation than other opioids, but larger studies have not confirmed this finding[29]

» Unique to methadone:

° Typically causes less euphoria than other opioids[14]

° Dose-dependent QTc interval prolongation (may also occur with buprenorphine)[27, 30]

› We do not recommend EKG monitoring in hospice patients receiving methadone or for whom methadone is being considered.

› Risk factors include: high dose, IV route, hypokalemia, low prothrombin, impaired liver function, structural heart disease, co-administration of CYP3A4 inhibitors, advanced age)

› The level of concern / vigilance with regard to methadone-induced QTc interval prolongation should consider patient prognosis and methadone's place in therapy (ie, more vigilant in non-terminally ill patients when methadone being used as first line therapy; less vigilant in hospice patients when other opioids have failed and methadone is not first line therapy)[31]

› Avoid concomitant use of other medications that prolong the QTc interval

° Hypoglycemia is possible (may also occur with tramadol).[32–35] Do not avoid methadone use for this reason, but consider methadone-induced hypoglycemia a possibility if unexplained hypoglycemia occurs.

DOSING

- Methadone dosing frequency

» When using for chronic pain, methadone is ideally dosed every 8 hours

» Twice daily dosing is acceptable if needed to ensure patient compliance

» Daily dosing is acceptable with low doses during initial therapy, but if higher doses are given, daily dosing is typically only used in opioid treatment programs

- Methadone prescriptions with higher doses and once daily dosing, often with odd doses (eg, 85mg daily), should be a red flag to hospices and pharmacists that the prescription may be for opioid maintenance, rather than for chronic pain treatment.[8]
  - It is unlawful for a pharmacist to dispense a prescription for methadone if it is being used for opioid maintenance and the prescriber lacks an "X-waiver" in their DEA number.
  - When writing prescriptions for methadone for chronic pain, prescribers are not required to write "for pain" on the prescription.
  - For methadone maintenance patients who also have chronic pain, it is permissible for the pharmacist to fill the methadone prescription, even if the prescriber lacks the X-waiver, but it is advisable that they insist that "for pain" be included on the prescription when methadone is being used for this dual purpose.

- Initial methadone dosing
  - For treatment of chronic pain[27 – 28]
    - 2.5mg daily to three times daily
    - For frail/ elderly patients, doses as low as 1mg daily may be used[17]
- Use in breakthrough pain
  - OnePoint Patient Care does not support the use of methadone for breakthrough pain or on an "as needed" basis.[15, 28]
- Converting to methadone from other opioid(s)
  - Convert all non-morphine opioids to oral morphine equivalents (OME) first
  - Methadone safety guidelines advise against converting to daily methadone doses greater than 40mg per day, regardless of the method used to convert to methadone[11]
    - For complex cases, or when 40mg/day is exceeded, admission to a hospice in-patient unit is reasonable to monitor the conversion process[8]
  - OnePoint Patient Care endorses two methods to convert from OME to oral methadone
    - Dynamic ratio method (AAHPM version) (**Table 1**)

TABLE 1 – DYNAMIC RATIO METHOD FOR CONVERTING TO METHADONE (AAHPM VERSION)

24-HOUR OME (MG)	CONVERSION RATIO (OME: ORAL METHADONE)
<30	2:1
31 – 99	4:1
100 – 299	8:1
300 – 499	12:1
500 – 999	15:1
1,000 – 1,200	20:1
> 1,200	Consider Expert Consult

      - Divide OME by the corresponding conversion ratio provided by the table to give daily methadone amount needed
      - Divide the 24-hour amount by three, then round to nearest appropriate amount per dose
      - When starting with more than 1,200mg OME, it is reasonable to use a higher ratio (ie, 25 or 30:1)
      - Break points between listed ratios is a limitation to this method (eg, 100mg OME should convert to a higher daily methadone amount than 99mg OME).[39] As such, it is reasonable to modify the conversion ratio (eg, use a 6:1 ratio when converting from 100mg OME)
    - Rule of 15's (aka Plonk method)[40]
      - Closely approximates the Fudin equation[39] (a function of best fit using experimental data points from clinical methadone conversion studies), but more practical to use
      - Daily methadone (mg) = (daily OME (mg)/ 15) + 15
      - Valid for OME 60 to 1,200mg per day
    - We advise against "as-needed" use of methadone (eg, Morley Makin method, etc.) to calculate maintenance dosing
- Timing of conversions from another opioid to methadone

» Regardless of the timing of the conversion, patients may experience temporary worsening of pain control (we recommend use of short-acting opioid as needed during this period)
» The conversion is typically accomplished in one of two ways: [24, 41 – 43]
  ° Stop and go: stop previous opioid and start methadone at calculated dose when next dose of previous opioid would have been administered
    › Simpler method which may reduce the chance of administration errors
    › Possibly associated with more adverse effects / worsening pain than 3-day cross taper method [24, 42 –43]
    › Recommended method if switching to methadone due to toxicity of previous opioid [41]
  ° 3-day cross taper: more complex method where previous opioid is tapered to discontinuation over three days in increments of one-third while simultaneously titrating methadone, starting at one-third of the calculated amount and titrating by one-third increments over three days.
    › Often requires use of multiple medication strengths with individual prescriptions for each strength, which can result in administration errors [8]
    › Patients may experience better pain control and fewer adverse effects during the initial conversion process [24, 42 – 43]
    › Possibly preferential for patients being converted to methadone from high oral morphine equivalent (OME) (>300mg OME) [42]

- Converting from methadone to another opioid
  » The clinical rationale for this conversion should be questioned as escalation of pain and dysphoria are common, despite titration of new opioid (pitfalls)
  » When possible, use the previous non-methadone opioid dose as a guide
  » If unavailable, using a 3:1 morphine:methadone ratio is considered safe [1]
    ° The actual conversion ratio may be as high as 5 to 1 (5:1) or 6 to1 (6:1) [1]
- Titration of methadone
  » Because time to steady state is about 4-5 half-lives (4-5 days), do not titrate methadone more often than every 5 days [11]
  » With the exception of doubling from 2.5 to 5mg per dose, numerical doubling (as is done in patients with severe pain who are receiving other opioids) of the methadone dose is rarely indicated.
  » Gradual titration of methadone by small increments is preferred [11, 45]
    ° Increase by 2.5mg per dose at lower doses
    ° May increase by 5mg per dose at higher doses

MONITORING

- Monitoring parameters
  » Patient and caregiver education can help reduce methadone-related adverse effects and fatalities from overdose [48 – 49]
    ° The U.S. Department of Health & Human Services has downloadable information for patients and caregivers regarding the safe use of methadone (https://store.samhsa.gov/shin/content//SMA09-4409/SMA09-4409.pdf)
  » The risk of methadone overdose is highest during initiation, titration or when drugs that inhibit methadone metabolism are added
    ° We recommend daily formal monitoring of both methadone efficacy and toxicity during these times (**Figure 1**)
      › Whether monitoring is done in person or via phone should consider patient-specific monitoring environment and caregiver capabilities. Home visits may not be needed if the hospice team is able to speak to a reliable adult. [17]
  » CNS depression will precede severe overdose / chronic methadone toxicity
    ° Early signs of toxicity: drowsiness, euphoria, ataxia, slurred speech
      › Methadone should be held if excessive sedation occurs and reintroduced cautiously at a lower dose [15]
    ° Later signs of toxicity: respiratory depression, pin point pupils, loss of consciousness, loud snoring, brown pulmonary edema secretion

» Methadone does not typically reach full efficacy until after about 5 days (after steady-state concentration reached). Near immediate pain improvement (1 – 2 days) after initiating methadone therapy can, but does not always, indicate impending toxicity. Close monitoring is recommended in these circumstances. [15, 37]

FIGURE 1 – SUGGESTED METHADONE THERAPY MONITORING

MONITORING PARAMETER	DAY 0*	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Therapeutic Effectiveness								
Pain Rating (0-10) – Best in Past 24 Hours								
Pain Rating (0-10) – Worst in Past 24 Hours								
Pain Rating (0-10) – Average in Past 24 Hours								
No. of Opioid Doses For Breakthrough Pain								
Able to Perform Activities of Daily Living (ADLs)?								
Potential Toxicity (New or Worsening): RAPS								
R – Respirations Slowed or Irregular								
A – Altered Mental Status or Vision								
P – Pupils, Palpitations/ Lightheadedness								
S – Snoring, Sedation								
General Opioid Adverse Effects (Constipation, Nausea, Urinary Retention, Itching, Dry Mouth)								

* Day 0 – refers to patient status prior to first dose of methadone. Day 1 refers to 24 hours after beginning methadone and so on.

References

1. McPherson, ML, Demystifying Opioid Conversion Calculations – A Guide for Effective Dosing, American Society of Health-System Pharmacists, 2010.
2. Muijsers, R. et al. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control, Drugs, 2001; 61(15):2289-307.
3. Duragesic prescribing information, Janssen Pharmaceuticals, Inc., accessed online at: https://www.janssenmd.com/pdf/duragesic/duragesic_pi.pdf, last updated March 2017.
4. Lexicomp, Fentanyl monograph section on Pharmacodynamics/Kinetics; half-life elimination of transdermal fentanyl patch.
5. Medication Guide – Fentanyl Transdermal System, CII, Mallinckrodt Pharmaceuticals, Revised October 2014.
6. Fentanyl Transdermal, Facts & Comparisons eAnswers, accessed online May 2017.
7. Raj Bista, S. et al. Validation of a Fentanyl Transdermal Adhesion Scoring Tool for Use in Clinical Practice, J of Pain and Symptom Management, 2015;49(5):934.
8. Authors' experience
9. Heiskanen, T. et al. Transdermal fentanyl in cachectic cancer patients, Pain, 2009;144:218-22.
10. Suno, M. et al. Refractory cachexia is associated with increased plasma concentrations of fentanyl in cancer patients, Therapeutics & Clin Risk Management, 2015;11:751-7.
11. Chou, R. et al. Methadone Safety: A Clinical Practice Guideline From the American Pain Society and College on Problems of Drug Dependence, in Collaboration With the Heart Rhythm Society, The Journal of Pain, 2014;15(4):321-37.
12. Jones, C. et al. Trends in methadone distribution for pain treatment, methadone diversion, and overdose deaths – United States, 2002-2014, Morbidity and Mortality Weekly Report, 2016;65(26):667-71.
13. Haumann, J. et al. Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer, Eur J of Cancer, 2016;65:121-29.
14. Barbosa Neto, J. et al. Revisiting methadone: pharmacokinetics, pharmacodynamics and clinical indication, Rev Dor Sao Paulo, 2015;16(1):60-6.
15. Cimino, N. et al. Practical guide to the safe use of methadone, Practical Pain Management, 2015;15(2):1-11.
16. Davis, M. et al. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration, Support Care Cancer, 2001;9:73-83.
17. BPAC.org, WHO analgesic ladder: step 3 – methadone safe and effective use for chronic pain, Best Practice Journal, Issue 18, 2008.
18. Sylvester, R. et al. Evaluation of methadone absorption after topical administration to hospice patients, J of Pain & Symptom Management, 2011;41(5):828.
19. Kapur, B. et al. Methadone: a review of drug-drug and pathophysiological interactions, Crit Rev in Clin Lab Sciences, 2011;48(4):171-95.
20. Tesseromatis, C. et al. Acute-Phase proteins: alpha-1-acid glycoprotein, 2011, accessed online May 2017 at: http://cdn.intechopen.com/pdfs/21455/InTech-Acute_phase_proteins_alpha_1_acid_glycoprotein.pdf
21. Eap, C. et al. Interindividual variability of the clinical pharmacokinetics of methadone, Clin Pharmacokinetics, 2002;41(14):1153-93.
22. Ferrari, A. et al. Methadone – metabolism, pharmacokinetics and interactions, Pharmacological Research, 2004;50:551-9.
23. Kharasch, E. Current concepts in methadone metabolism and transport, Clinical Pharmacology, 2017;6(2):125-34.
24. McLean, S. Methods of rotation from another strong opioid to methadone for the management of cancer pain: a systematic review of the available evidence, J of Pain Symptom Management, 2015;50(2):248.
25. Ahmad, T. et al. Tell-tale SNPs: the role of CYP2B6 in methadone fatalities, J of Analytical Toxicology, 2017;41:325-333.
26. Lugo, R. et al. Pharmacokinetics of methadone, J of Pain & Palliative Care Pharmacotherapy, 2005;19(4):13-24.
27. Chou, R. et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in Collaboration with the Heart Rhythm Society, The Journal of Pain, 2014;15(4):321-37.
28. Mallinckrodt Pharmaceuticals, Methadone package insert, last revised April 2015.
29. Daeninck, P. et al. Reduction in constipation and laxative requirement following opioid rotation to methadone: a report of four cases, J Pain Symptom Management, 1999;18(4):303.
30. Buprenorphine, Lexicomp.
31. McPherson, ML et al. Consensus guidelines for methadone safety and effectiveness in hospice and palliative care, 2016 AAHPM & HPNA Annual Assembly.
32. Flory, J. et al. Methadone use and the risk of hypoglycemia for inpatients with cancer pain, J Pain Symptom Management, 2015, article in press.
33. Faskowitz, A. et al. Methadone-induced hypoglycemia, Cell Mol Neurobiol, 2013;33:537-42.
34. Fournier, JP et al. Tramadol use and the risk of hospitalization for hypoglycemia in patients with Noncancer pain, JAMA Intern Med, 2015;175(2):186-93.
35. Nelson, L. et al. Tramadol and hypoglycemia – one more thing to worry about, JAMA Intern Med, 2015;175(2):194.
36. Manfredonia, JF, Using methadone to control pain in patients during final stages of life, J Am Osteopath Assoc, 2007;107(suppl 4):ES17.
37. American Academy of Hospice and Palliative Medicine (AAHPM) Palliative Care Primer, 2010, accessed online at: http://www.compassionandsupport.org/pdfs/professionals/pain/Methadone_Dose_Conversion_Guidelines.051810_.pdf
38. Burgess, F. et al. Methadone analgesia: balancing the risks and benefits, Pain Medicine News, December 2009, pp. 101.
39. Fudin, J. et al. Mathematical model for methadone conversion examined, Practical Pain Management, September 2012, pp. 46.
40. Plonk, W. Simplified methadone conversion, J of Pall Med, 2005;8(3):478-9.
41. Prommer, E. Methadone for cancer pain, Palliative Care: Research and Treatment, 2010;4:1-10.
42. Moksnes, K. et al. How to switch from morphine or oxycodone to methadone in cancer patients? A randomised clinical phase II trial, Eur J of Cancer, 2011;47:2463-70.
43. Bourke, AM et al. Variations in methadone prescribing and outcomes – a service evaluation in Sheffield and Chesterfield, BMJ Supportive & Palliative Care, 2014;4(Suppl 1):A51.
44. Moryl, N. et al. Pitfalls of opioid rotation: substituting another opioid for methadone in patients with cancer pain, Pain, 2002;96:325-328.
45. VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain, Version 3.0 – 2016.
46. Gallagher, R. Opioid-induced neurotoxicity, Canadian Family Physician, 2007;53:426.
47. Serotonin syndrome, mayoclinic.org, accessed online June 2017 at: http://www.mayoclinic.org/diseases-conditions/serotonin-syndrome/symptoms-causes/dxc-20305673
48. Baxter, L. et al. Safe methadone induction and stabilization – Report of an expert panel, J Addict Med, 2013;7(6):377.
49. U.S. Department of Health & Human Services, Follow Directions: How to use Methadone Safely, accessed online June 2017 at: https://store.samhsa.gov/shin/content//SMA09-4409/SMA09-4409.pdf

Naloxone

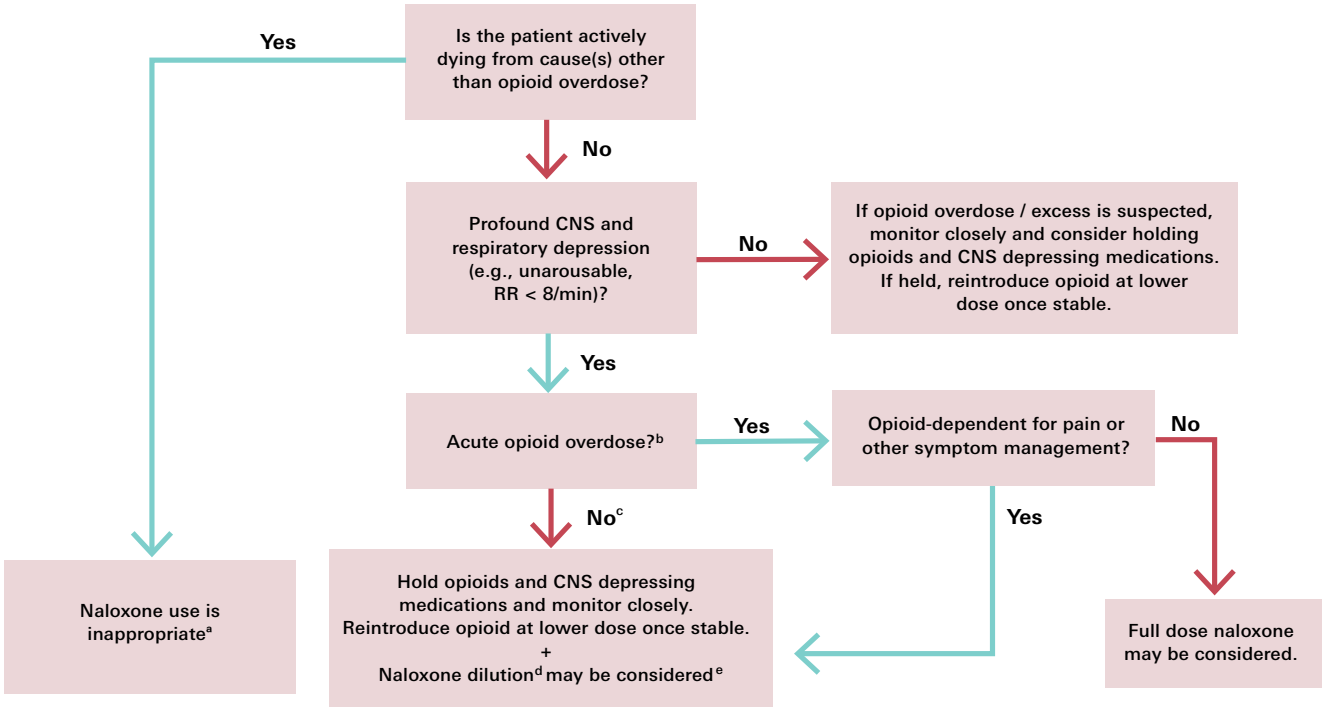
INTRODUCTION

- The opioid crisis in the U.S. causes tens of thousands of deaths per year due to overdose. State and Federal agencies and legislators have developed, and continue to develop policies, guidelines, and statutes that aim to curb this epidemic.
- Central amongst these endeavors is naloxone (Narcan®), an opioid reversal agent which saves thousands of lives per year.
  - » In those who have received opioids (either prescribed or illicit) it reverses both beneficial (e.g., analgesia, relief from dyspnea) and harmful (e.g., respiratory & CNS depression) opioid effects.
  - » Opioid abstinence / withdrawal syndrome occurs following naloxone administration in patients who have received opioids and now experience the opposites of typical opioid effects (i.e., pain crises vs. pain relief; diarrhea vs. constipation; dysphoria vs. euphoria).[1-2]
  - » Naloxone has no effect when given to patients who have not received opioids.

APPROPRIATE USE OF NALOXONE IN HOSPICE PATIENTS

- While life-saving in most contexts, inappropriate naloxone use in hospice patients can cause great discomfort and, in rare cases, may even cause death due to cardiovascular collapse.[1]
- Special considerations are required to justify the use of naloxone in the hospice population, for whom naloxone administration is rarely indicated.
  - » Each clinical scenario is unique and, although rare, naloxone use is warranted in some cases, even in terminally ill patients.[3]
- Appropriateness depends on several factors (**Figure 1**):
  - » Disease trajectory / prognosis
  - » Amount and timing of opioid dose(s) received
  - » Degree of respiratory and CNS compromise

FIGURE 1: OPPC NALOXONE DECISION MAKING ALGORITHM



a - Naloxone will not prevent death and will likely cause significant discomfort
b - Implies patient received an opioid dose that was grossly higher than prescribed (e.g., received 5ml instead of 5mg)
c - Implies a clinical scenario of opioid excess with chronic dosing
d - 0.4mg of naloxone diluted 10-fold with saline and administered IV/SQ in smaller 0.04mg dose aliquots (see drug information table) by hospice clinician
e - This strategy can facilitate increased respirations and level of consciousness without sacrifice of opioid-managed symptom control

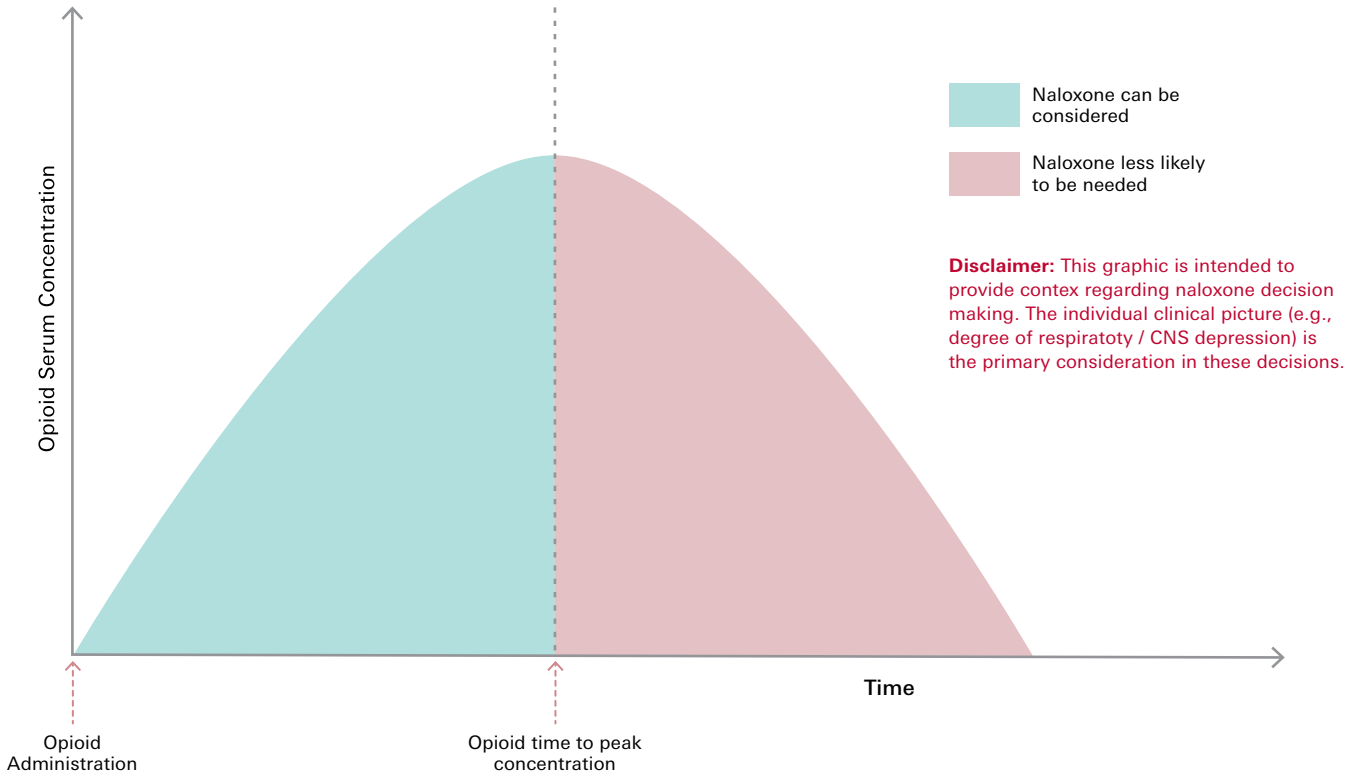
NALOXONE DOSAGE FORM SELECTION

- All commercially available naloxone dosage forms are effective at reversing opioid effects when used according to their product labeling.
- Consider cost, convenience, as well as caregiver preference and administration capability when selecting a naloxone dosage form.
- Improvised intranasal naloxone can be assembled by attaching an intranasal atomizer to a Luer-lock syringe containing the solution for injection.
  - » Requires more frequent administrations and results in lower blood levels compared to using as recommended by the manufacturer in the product labeling.[4]
  - » Caregivers are five times less likely to administer properly, even with coaching.[4]

PHARMACOKINETIC CONSIDERATIONS

- Knowledge of which opioid is implicated in overdose and the dosage form taken or administered can play a crucial role in the handling of the overdose event. In particular, time to peak concentration and duration of effect should be considered (See appendix – Opioid and Benzodiazepine Kinetics Tables).
- Symptoms of opioid overdose correlate directly with opioid serum concentrations.
  - » If the time since opioid overdose is known, and is shorter than the involved opioid's time to peak concentration, the overdose symptoms will continue to worsen until time to peak is reached. In this scenario, naloxone use may be considered.
  - » If the time since overdose is longer than the time to peak and the patient's respiratory rate is stable, the most dangerous part of the overdose has passed and naloxone is unlikely to be needed (**Figure 2**).

FIGURE 2: CONSIDERING OPIOID TIME TO PEAK EFFECT IN DECISION WHETHER TO ADMINISTER NALOXONE

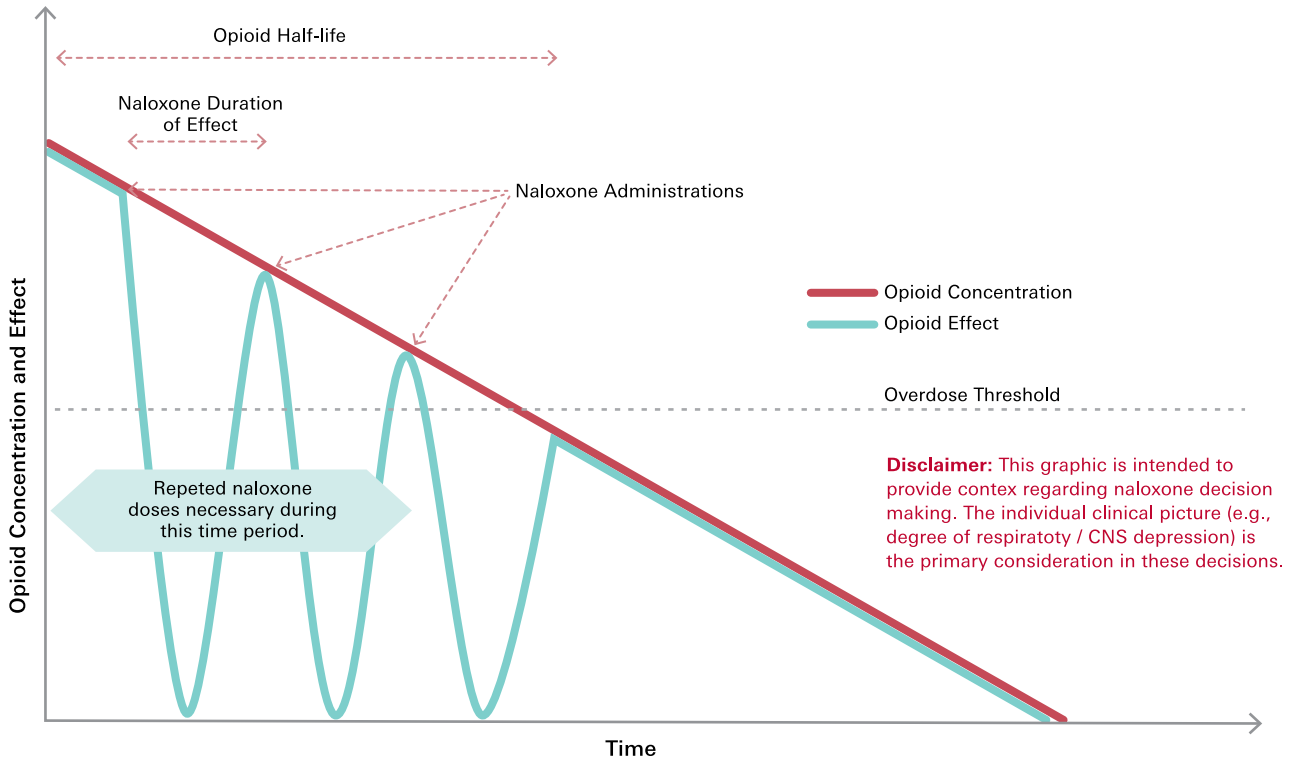


- Initial response to naloxone implicates opioid overdose, but subsequent doses are often needed (**Figure 3**).
  - » Most opioids, including short-acting formulations, have durations of effect that considerably exceed the typical 30 to 120 minute duration of naloxone.[2]
  - » In particular, overdoses involving methadone, buprenorphine, and extended release opioids are more likely to require multiple naloxone doses.
  - » Continuous infusions of naloxone may be needed in some circumstances, which may require hospitalization.
- If the initial naloxone dose does not reverse respiratory depression, subsequent doses can be administered (see dosing in Drug Information table). However, failure to respond to several sequential doses should prompt consideration of other, non-opioid causes of respiratory depression.

PREEMPTIVE PLACEMENT OF NALOXONE IN PATIENT RESIDENCES

- In some circumstances, it is reasonable to preemptively place naloxone in patient residences, such as when the patient or their family / caregiver are deemed to be at high risk for opioid overdose.
- Risk stratification tools like the Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression (RIOSORD) exist to aide in these decisions, but have not been validated for use in hospice patients.
- Factors that weigh in favor of preemptive placement in the hospice setting include:[3]
  - » Patient / family / caregiver history of opioid overdose or substance use disorder, including alcohol
  - » Relatively long prognosis (i.e., several months vs. days)

FIGURE 3: CONSIDERING OPIOID AND NALOXONE DURATIONS OF EFFECT IN DECISION TO REPEAT NALOXONE DOSES



- » High opioid dose (note: Centers for Disease Control guidance cites opioid doses exceeding 50mg oral morphine equivalent (OME) as a risk factor, although they specifically mention the recommendation should not be applied to cancer, palliative care, or hospice patients)[5]
- » Rapid opioid titration
- » Teenagers or small children in residence
- » Patient resides in a remote location where it would not be possible to receive naloxone in a timely manner if needed
- » Concomitant use of other CNS depressing drugs (e.g., benzodiazepines, muscle relaxants, gabapentinoids)

CLINICAL PEARLS REGARDING NALOXONE ADMINISTRATION IN THE HOSPICE SETTING

- Caregivers should contact hospice immediately if a patient overdoses on opioids. Decisions about calling 911 or performing CPR should ideally be collaborative decisions with hospice that consider current goals of care and code status.
- Verify no additional opioids or sedatives are administered. Stop any infusions of these drugs and verify any transdermal opioid patches like fentanyl or buprenorphine are removed.
- Differentiation between the natural dying process and opioid overdose can be difficult.
  - » Pinpoint pupils that are poorly responsive to light occur with opioid overdose, but not during the dying process.
  - » Cheyne-Stokes breathing (breathing pattern characterized by random, alternating periods of hyperventilation and apnea) often occurs during the dying process. In contrast, respiratory depression / slowed respirations occur with opioid overdose.
- The goal of naloxone administration is reversal of respiratory depression, not reversal of CNS depression/somnolence.

DRUG INFORMATION

GENERIC NAME (BRAND NAME)	USUAL STARTING DOSE AND RANGE	STRENGTHS AND FORMULATIONS	COMMENTS	CRUSH/ OPEN?
Naloxone (Narcan Nasal)[2]	Full opioid reversal: Initial (intranasal): 4mg (one device) into one nostril; may repeat dose in alternating nostril every 2-3 minutes MDD: If no response after several doses, consider alternate, non-opioid causes of respiratory depression	Nasal spray: 4mg/0.1mL	• Dispensed with two devices • Do not prime or test device • Cannot be used for partial reversal	-
Naloxone (Narcan)[2]	Full opioid reversal: Initial (IV/SQ/IM): 0.4-2mg PRN; may repeat doses every 2-3 minutes MDD: If no response after cumulative 10mg dose, consider alternate, non-opioid causes of respiratory depression Partial opioid reversal:[1] Initial (IV/SQ): 1ml (0.04mg) of diluted naloxone solution (see instructions to right) every 1-5 minutes PRN	Solution for injection: 0.4mg/ml (single/ multi-dose vial, ampule, Carpuject™ Single-use cartridge system), 2mg/2ml (prefilled single use Min-I-Jet™ system syringe) Preparation of diluted naloxone solution:[1] Dilute 1ml of 0.4mg/ml naloxone with 9ml normal saline to prepare 10ml of 0.04mg/ml naloxone solution	• The anterolateral thigh is the preferred site for IM administration. • Must determine if full or partial opioid reversal desired (see OPPC algorithm in monograph – Figure 1) • Administration of aliquots of diluted naloxone solution can facilitate partial opioid reversal without causing pain crises in opioid-dependent patients[1] • Dosage forms other than single / multi-dose vials cannot be used for partial reversal. • Naloxone auto-injector forms have been discontinued by manufacturer	-

References

1. Arnold, R et al. Using Naloxone, Palliative Care Network of Wisconsin Fast Facts and Concepts #39, accessed via mobile application April 2019.
2. Lexicomp 2019, Naloxone monograph.
3. Chwistek, M et al. Naloxone for Outpatients at Risk of Opioid Overdose, Palliative Care Network of Wisconsin Fast Facts and Concepts #328, accessed via mobile application April 2019.
4. Krieter, et al. Comparison of the Pharmacokinetic Properties of Naloxone Following the use of FDA-approved Intranasal and Intramuscular Devices Versus a Common Improvised Nasal Naloxone Device, J Clin Pharm, 2019 March.
5. Center for Disease Control (CDC) Checklist for prescribing opioids for chronic pain, accessed online Dec. 2019 at: https://www.cdc.gov/drugoverdose/pdf/pdo_check-list-a.pdf

OnePoint®
PATIENT CARE

What one can do.®

Appendix

Relatedness & Medication Coverage

INTRODUCTION AND OVERVIEW

- **realm** – a field or domain of activity, a particular area of knowledge or experience
- **related** – belonging to the same family, group or type; connected
- **relatedness** – connected by reason of an established or discoverable relation

According to CMS, under the Medicare Conditions of Participation §418, "hospices are responsible for covering drugs and biologicals related to the palliation and management of the terminal illness and while the patient is under hospice care. For a prescription drug to be covered under Part D for an individual enrolled in hospice, the drug must be for treatment unrelated to the terminal illness or related conditions." It is the expectation of CMS that hospices' "should be providing virtually all of the care needed by terminally ill individuals, including related prescription drugs. The comprehensive nature of the services covered under the Medicare hospice benefit is structured such that hospice beneficiaries should not have to routinely seek items, services, and/or medications beyond those provided by hospice."[1]

Each year, CMS publishes their Hospice Wage Index and Payment Rate Update and Hospice Quality Reporting Requirements (herein referred to as Guidance). Within these rules are reports on trends in the growth of Medicare Hospice utilization such as overall expenditures, non-hospice spending during a hospice election and changes in diagnosis patterns. Most notable is information and various analyses on Medicare Part D utilization and spend. It is important to understand the potential impact of these analyses, most significantly the potential for changes to hospice payment rates or payment policies.

Recent analysis of non-hospice Part D spend for patients that had elected the Hospice Benefit caused identified a non-trivial amount of spend. As a result CMS has, over a number of years refined and clarified its expectations for hospice coverage of medication under the benefit. Over those years, Guidance has ranged from general (ie, hospice is expected to cover specific classes of medications such as analgesics, anxiolytics, anti-emetics and laxatives for all patients) to specific (hospice is expected to cover drug "x" for condition "y"). It is important to recognize that CMS views its Guidance interventions as having reduced Part D program payments.

Essential to appropriate drug coverage decisions and the resulting reduction in non-hospice Part D spend as well as reducing the potential for regulatory changes regarding drug provision under the benefit is a solid understanding of relatedness. This chapter of the Guide contains three sections related to the topic.

HOW TO USE THIS CHAPTER

RELATEDNESS & HOSPICE RESPONSIBILITY ALGORITHMS

The first section is to assist our partners in navigating drug coverage decision making. Here we present NHPCO's Relatedness Algorithm. To that we have added our Hospice Medication Payment Responsibility Algorithm.

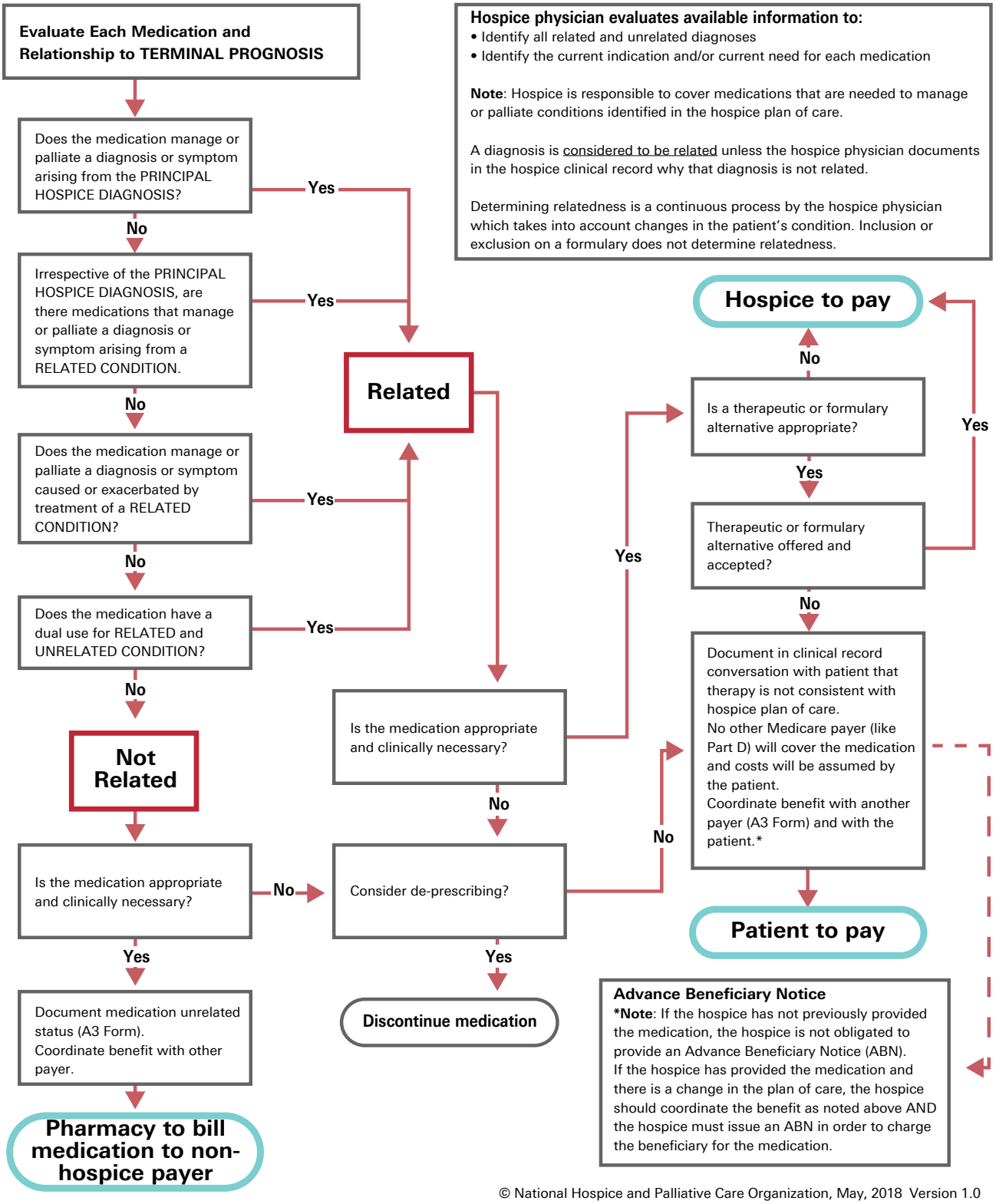
WAGE INDEX GUIDANCE

The second section is to assist our partners in tracking and understanding coverage expectations. We have created a comprehensive table outlining the chronologic changes to drug coverage Guidance for Fiscal Years 2015-2020. For ease of application with other OnePoint tools they are presented in a manner congruent with our Disease State and Preferred Drug List constructs.

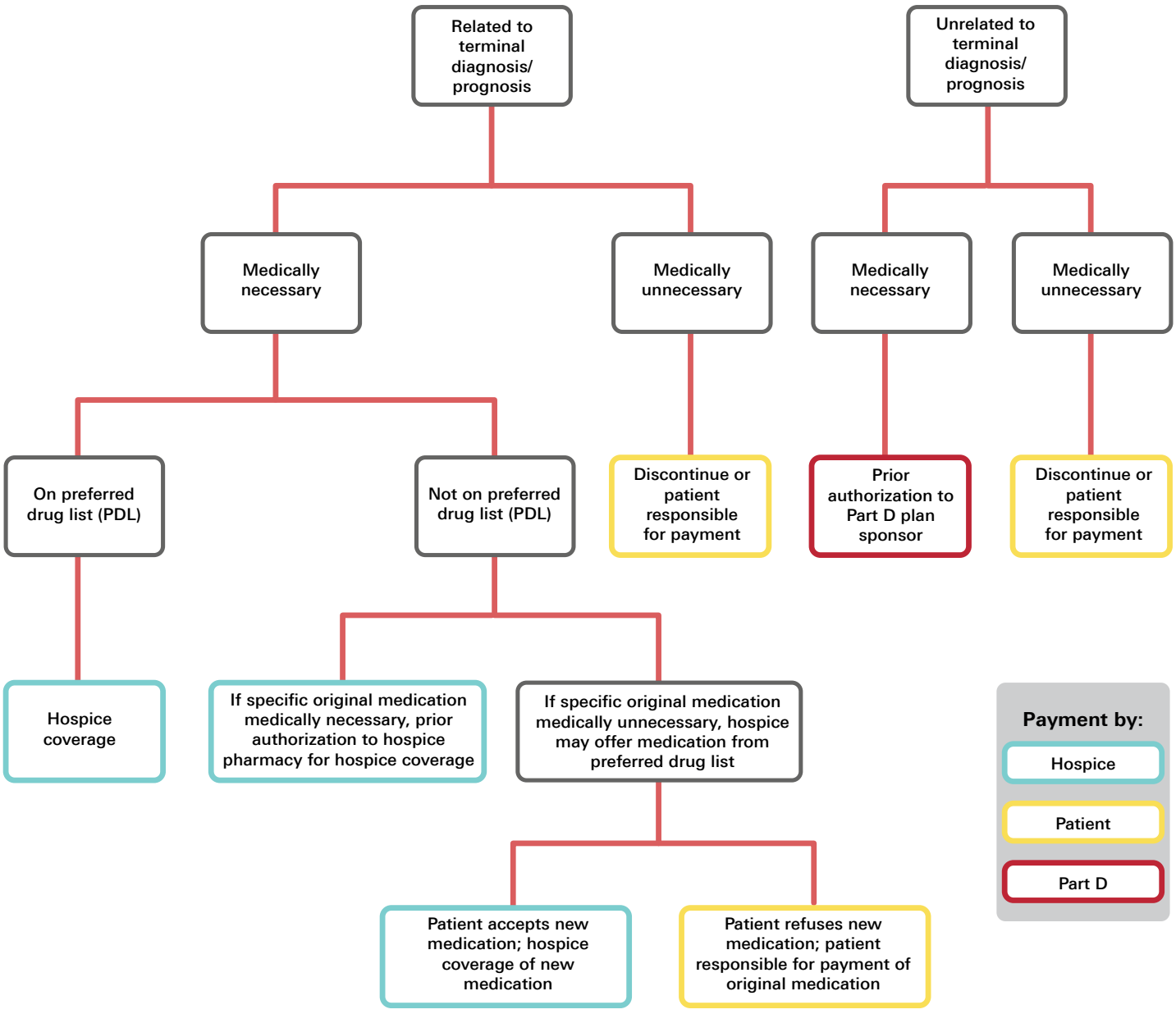
NHPCO RELATEDNESS ALGORITHM [A]

Determination of Hospice Medication Coverage

National Hospice and Palliative Care Organization



HOSPICE MEDICATION PAYMENT RESPONSIBILITY ALGORITHM



COMBINED WAGE INDEXES FY 2015-2020

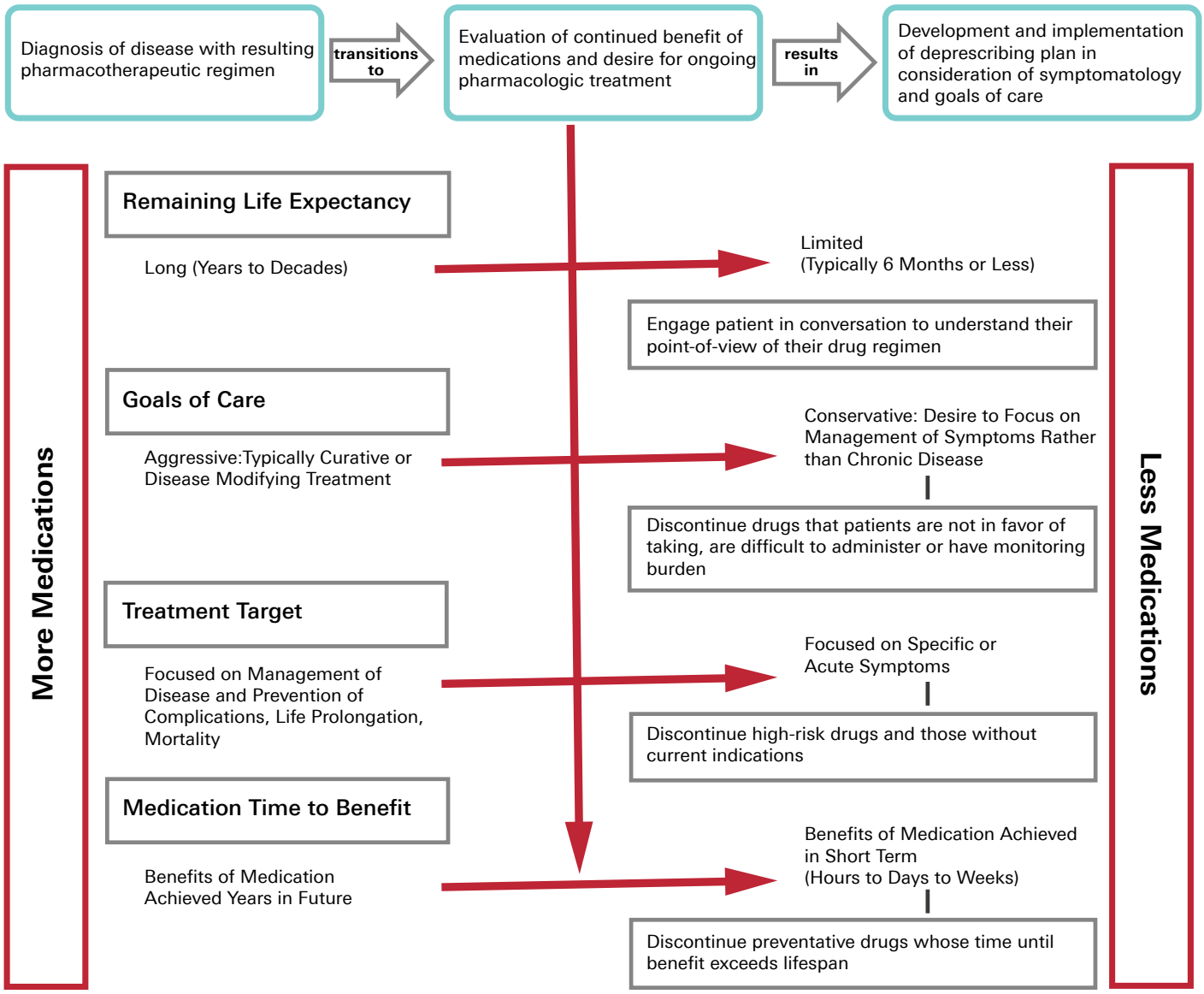
OPPC DISEASE STATE	WI YEAR	GUIDANCE (DRUGS OR DRUG CLASSES IDENTIFIED AS RELATED)
All Patients	2015	Analgesics are related. CMS did not specifically define analgesics. The following classes have labeled indications for the treatment of pain: opioids, corticosteroids, anti-inflammatory drugs, non-narcotic analgesics, topical analgesics, topical anesthetics and select SNRIs (duloxetine). Other classes that are used off-label to treat pain include: TCAs, other SNRIs, anticonvulsants, clonidine, and fluoxetine.
	2015	Antiemetics are related. CMS did not specifically define antiemetics. The following classes have labeled indications for the treatment of nausea and vomiting: select antipsychotics (olanzapine, prochlorperazine, chlorpromazine), antihistamines, anticholinergics, 5HT-3 antagonists, gastrointestinal stimulants and corticosteroids. Other classes that are used off-label include other antipsychotics (haloperidol, quetiapine) and hydroxyzine.
	2015	Anxiolytics are related. CMS did not specifically define anxiolytics. The following classes have labeled indications for the treatment of anxiety: benzodiazepines, non-benzodiazepine anxiolytics, antihistamines, select SSRIs/SNRIs. Other classes that are used off-label include TCAs, other SSRIs/SNRIs, and anticonvulsants.
	2015	Bowel care is related. CMS did not specifically define bowel care. The following classes have labeled indications for the treatment of constipation: stimulant laxatives, bulk-forming agents, lubricants, sufactant laxatives, osmotic laxatives, saline laxatives, combination products, chloride channel activator (lupiprostone), and peripheral opioid antagonists. Other drugs that are used off-label include erythromycin and misoprostol
	2020	CMS provided examples of maintenance drugs / supplies appropriate for continuation when they aid in relief of symptoms; examples include diabetic test strips to aid in blood glucose control and prevention of hyperglycemia symptoms, BPH medication (tamsulosin) for urinary retention in a septic patient, and palliative chemotherapy / radiation / blood transfusions.
Cancer	2016	Cancer of trachea, bronchus or lung: common symptoms include cough, dyspnea, pain, chest pain, metastatic bone pain, anorexia, weight loss, fatigue, depression. Drugs cited by CMS to manage these symptoms were NSAIDs, opioids, corticosteroids, antidepressants, palliative chemotherapy, bronchodilators, and anxiolytics (2016 WI). Other classes of drugs that were implied, but not explicity mentioned include antianginal, antitussive, psychostimulants, and progestins.
	2017	All cancer diagnoses: antineoplastics
	2017	Pancreatic cancer: pancreatic enzymes
Circulatory	2016	Heart failure: drugs used to treat dyspnea, edema, angina, cough, and fatigue, including: beta-blockers, ACE-inhibitors, ARBs, diuretics, antiplatelet agents, anticoagulants, and digoxin. Other classes of drugs that were implied but not explicity mentioned include: other antihypertensives, miscellaneous cardiovascular agents, antianginals, vasopressors, anti-tussives, psychostimulants.
	2017	Ischemic heart disease, other heart disease, stroke (acute & late effects): antianginals, antihypertensives, beta-blockers, calcium channel blockers, cardiotonics, miscellaneous cardiovascular agents, diuretics, miscellaneous hematological agents, and vasopressors.
	2017	Chronic renal failure: diuretics, hematological agents, minerals and electrolytes, nutrients, and vitamins.
	2018	CMS defined maintenance drugs, examples include drugs used to treat high blood pressure, heart disease, diabetes.

COMBINED WAGE INDEXES FY 2015-2020 (CONTINUED)

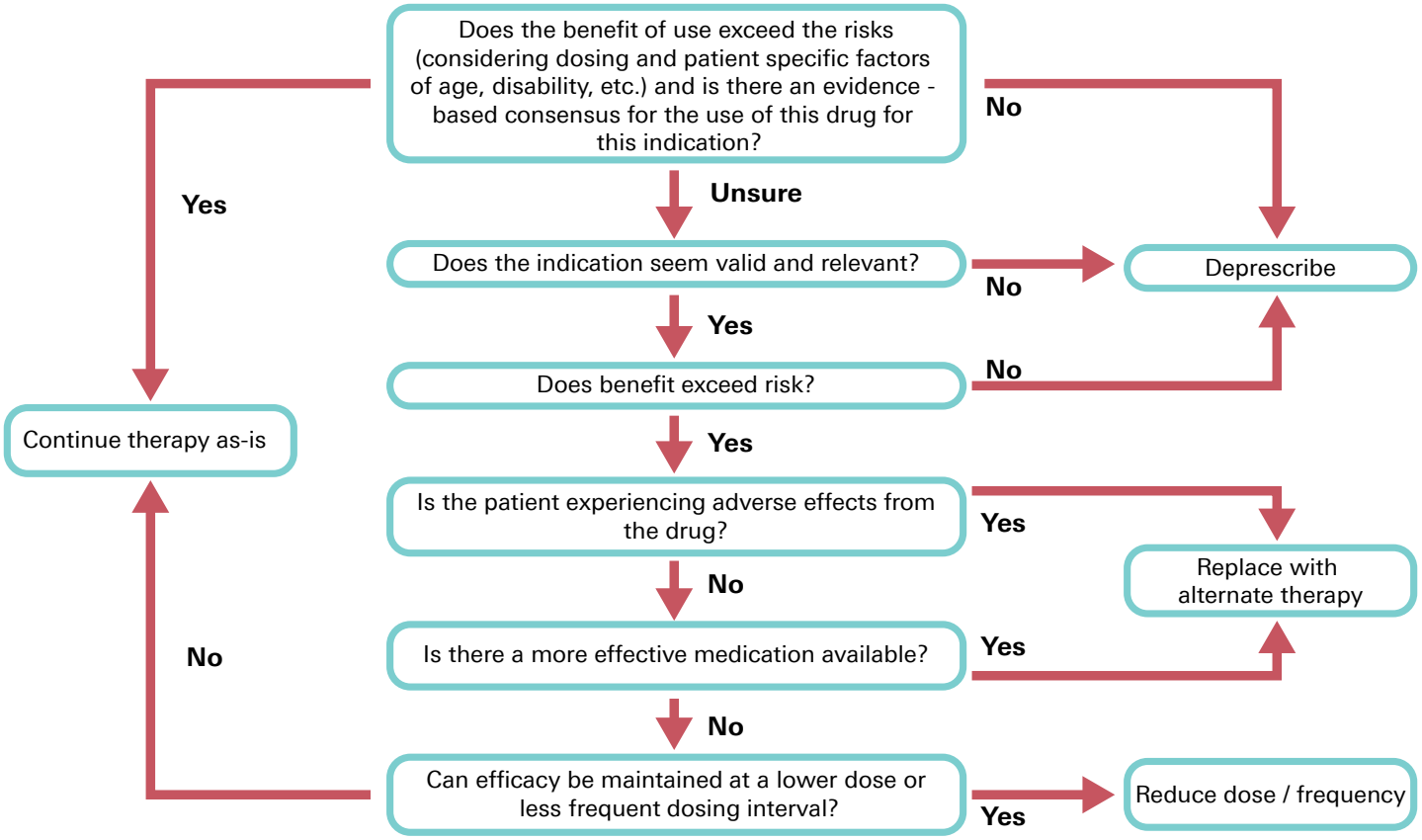
OPPC DISEASE STATE	WI YEAR	GUIDANCE (DRUGS OR DRUG CLASSES IDENTIFIED AS RELATED)
Lung	**2016**	Chronic airway obstruction: drugs used to treat shortness of breath, labored breathing, cough, increased heart rate, infections, and weight loss, including: opioids, antiasthmatics and bronchodilators, corticosteroids, and other respiratory agents. Other classess of drugs that were implied, but not explicity mentioned include: benzodiazepines, antibiotics, and anti-tussives.
	2017	COPD (chronic bronchitis, emphysema), lung diseases: antiasthmatics and bronchodilators, corticosteroids, and miscellaneous respiratory agents.
	2018	CMS defined maintenance drugs, examples include antiasthmatics.
Cerebral Degeneration	**2016**	Cerebral degeneration: drugs used to treat progressive loss of cognitive function, behavioral changes, personality changes, urinary and fecal incontinence, weight loss, muscle wasting, pneumonia, decubitus ulcers, and urinary tract infections, including: acetylcholinesterase inhibitors, memantine, antidepressants, antipsychotics, psychostimulants, mood stabilizers, benzodiazepines, and anti-manic agents. Other classes of drugs that were implied, but not explicity mentioned include: antibiotics, corticosteroids, progestins, analgesics, wound care products, and urinary antispasmodics.
	2017	Cerebral degeneration and mental disorders (senile & presenile): antimanics, antipsychotics, psychotherapeutics
	2017	Parkinson disease: antimanics, anti-Parkinson agents, antipsychotics, and psychotherapeutics
ESLD	**n/a**	No disease-specific advice from CMS in Wage Index and Quality Reporting guidance
Other	**n/a**	No disease-specific advice from CMS in Wage Index and Quality Reporting guidance

RATIONAL PRESCRIBING GRAPHIC[A]

Considerations for Deprescribing at End-of-Life



GARFINKEL/MANGIN DISCONTINUATION ALGORITHM [B]



BLEEDING ASSESSMENT – HAS-BLED [C]

HAS-BLED BLEEDING RISK EVALUATION		SCORING AND RISK	
Characteristic	Point Value	Total Score	Annual Bleed Risk (%)
Hypertension	1	0	1.13
Abnormal Renal or Hepatic Function (1 point each)	1 or 2	1	1.02
Stroke	1	2	1.88
Bleeding Tendency/ Predisposition	1	3	3.74
Labile INR (for patients taking warfarin)	1	4	8.70
Elderly (age > 65)	1	5 or higher	Insufficient Data
Drugs (concomitant aspirin or NSAID use) or alcohol abuse (1 point each)	1 or 2		

Data used in the development of this risk assessment excluded terminally Ill Patients

SPIESS MODEL FOR DISCONTINUING WARFARIN [D]

		HIGH RISK OF RETHROMBOSIS OR EMBOLISM?	
		Yes	No
HIGH BLEEDING RISK	Yes	Consider discontinuation of anticoagulation (risks typically exceed benefits)	Discontinue anticoagulation
	No	Continue anticoagulation and appropriate monitoring	Consider discontinuation of anticoagulation if consistent with current goals of care

HIGH RISK:

- VTE on warfarin < 3 months or with active cancer
- CHADS2 score ≥ 3 (sum of the following):
  - » Hypertension (1 point)
  - » Age ≥ 75 (1 point)
  - » Diabetes mellitus (1 point)
  - » Heart failure (1 point)
  - » Prior CVA (2 points)

HIGH BLEEDING RISK:

- Bleeding risk index ≥ 2 (2 or more of the following):
  - » Age ≥ 65
  - » Prior CVA
  - » Prior GI bleed
  - » Recent MI or hematocrit < 30% or SCr > 1.5mg/dL or diabetes mellitus
- Liver cirrhosis
- PPS ≤ 50%
- Nutritional impairment
- Drug interaction risk
- Poor compliance or labile INRs

References

1. Adapted from Holmes HM, Rational Prescribing for Patients With a Reduced Life Expectancy, Clin Pharmacology & Therapeutics, Vol 85 No 1 Jan 2009
2. Adapted from: Garfinkel D., et al. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: Addressing polypharmacy. Archives of Internal Medicine 2010; 170:1648.
3. Adapted from Lip, G. Implications of the CHA2DS2-VASc and HAS-BLED Scores for thromboprophylaxis in atrial fibrillation. Am J Med, 2011; 124:111.
4. Adapted from: Spiess, J., et al. Can I Stop the Warfarin? A Review of the Risks and Benefits of Discontinuing Anticoagulation. Journal of Palliative Medicine 2009 Vol. 12, No. 1.
5. Nicolle LE. Complicated urinary tract infection in adults. Can J Infect Dis Med Microbiol. 2005;16:349-60.

INHALED RESPIRATORY MEDICATION CHART

MEDICATION (GENERIC)	MEDICATION (BRAND)	INHALER NAME	DEVICE TYPE	TYPICAL FREQUENCY (HOURS)	OPTIMUM INSPIRATORY FLOW RATE FOR CLINICAL EFFECTIVENESS (L/MIN)	MINIMUM REQUIRED INSPIRATORY FLOW RATE FOR EFFECTIVENESS (L/MIN)	FOR LESS THAN MINIMUM REQUIRED FLOW CONSIDER SWITCHING TO:	REF
SHORT-ACTING BETA-2 AGONIST (SABA)								
Albuterol	ProAir	HFA	MDI	4 to 6	25-60	25	Albuterol nebulized solution	1
	Proventil	HFA	MDI	4 to 6	25-60	25		1
	Ventolin	HFA	MDI	4 to 6	25-60	25		1
	ProAir	Respiclick	DPI	4 to 6	60	30		2
	Albuterol	-	Neb	6 to 8	-	-		-
Levalbuterol	Xopenex HFA	HFA	MDI	4 to 6	25-60	25		1
	Xopenex	-	Neb	8	-	-		-
LONG-ACTING BETA-2 AGONIST (LABA)								
Arformoterol	Brovana	-	Neb	12	-	-	Albuterol nebulized solution (scheduled doses while awake)	-
Formoterol	Perforomist	-	Neb	12	-	-		-
Indacaterol	Arcapta	-	DPI	24	60	-		4
Olodaterol	Striverdi	Respimat	SMI	24	30	-		5
Salmeterol	Serevent	Diskus	DPI	12	60	30		6
INHALED SHORT-ACTING ANTICHOLINERGIC								
Ipratropium	Atrovent	HFA	MDI	6	25-60	25	Ipratropium nebulized solution	1
	Ipratropium	-	Neb	6 to 8	-	-		-

"Inhaled Respiratory Medication Chart (Tools for Alternative Therapy)"

Device Type Key

MDI	Metered Dose Inhaler
DPI	Dry Powder Inhaler
NEB	Solution for Nebulization
SMI	Soft Mist Inhaler

Tools for Alternative Therapy

OnePoint® PATIENT CARE

MEDICATION (GENERIC)	MEDICATION (BRAND)	INHALER NAME	DEVICE TYPE	TYPICAL FREQUENCY (HOURS)	OPTIMUM INSPIRATORY FLOW RATE FOR CLINICAL EFFECTIVENESS (L/MIN)	MINIMUM REQUIRED INSPIRATORY FLOW RATE FOR EFFECTIVENESS (L/MIN)	FOR LESS THAN MINIMUM REQUIRED FLOW CONSIDER SWITCHING TO:	REF
INHALED LONG-ACTING ANTICHOLINERGIC								
Aclidinium	Tudorza	Pressair	DPI	12	63	35	Ipratropium nebulized solution (scheduled doses while awake)	7
Glycopyrrolate	Seebri	Neohaler	DPI	12	50	50		17, 18
Revefenacin	Yupelri	-	Neb	24	-	-		13, 16
Tiotropium	Spiriva	Handihaler	DPI	24	20-60	20		8
	Spiriva	Respimat	SMI	24	30	-		5
Umeclidinium	Incruse	Ellipta	DPI	24	60	30		9
INHALED CORTICOSTEROID (ICS)								
Beclomethasone	QVAR	Redihaler	MDI	12	25-60	20	Oral Systemic corticosteroid (prednisone or dexamethasone)	1, 12
Budesonide	Pulmicort	Flexhaler	DPI	12	60	30		10
	Budesonide	-	Neb	12	-	-		-
Ciclesonide	Alvesco	HFA	MDI	12	25-60	25		1
Fluticasone Furoate	Arnuity	Ellipta	DPI	24	60	30		9
Fluticasone Propionate	Flovent	Diskus	DPI	12	60	30		6
	Flovent	HFA	MDI	12	25-60	25		1
Mometasone	Asmanex	HFA	MDI	12	25-60	25		1
	Asmanex	Twisthaler	DPI	12	30-60	30		11

"Inhaled Respiratory Medication Chart (Tools for Alternative Therapy)"

Device Type Key

MDI	Metered Dose Inhaler
DPI	Dry Powder Inhaler
NEB	Solution for Nebulization
SMI	Soft Mist Inhaler

MEDICATION (GENERIC)	MEDICATION (BRAND)	INHALER NAME	DEVICE TYPE	TYPICAL FREQUENCY (HOURS)	OPTIMUM INSPIRATORY FLOW RATE FOR CLINICAL EFFECTIVENESS (L/MIN)	MINIMUM REQUIRED INSPIRATORY FLOW RATE FOR EFFECTIVENESS (L/MIN)	FOR LESS THAN MINIMUM REQUIRED FLOW CONSIDER SWITCHING TO:	REF
COMBINATION SHORT-ACTING ANTICHOLINERGIC & SABA								
Ipratropium/ Albuterol	Combivent	Respimat	SMI	6	30	-	Ipratropium/albuterol nebulized solution	5
	Duoneb	-	Neb	6	-	-		-
COMBINATION LONG-ACTING ANTICHOLINERGIC & LABA								
Glycopyrrolate/ Formoterol	Bevespi	Aerosphere	MDI	12	25-60	25	Ipratropium/albuterol nebulized solution (scheduled doses while awake)	13, 14
Glycopyrrolate/ Indacaterol	Utibron	Neohaler	DPI	12	50	50		15, 18
Tiotropium/ Olodaterol	Stiolto	Respimat	SMI	24	30	-		5
Umeclidinium/ Vilanterol	Anoro	Ellipta	DPI	24	60	40		9

"Inhaled Respiratory Medication Chart (Tools for Alternative Therapy)"

Device Type Key

MDI	Metered Dose Inhaler
DPI	Dry Powder Inhaler
NEB	Solution for Nebulization
SMI	Soft Mist Inhaler

Tools for Alternative Therapy

OnePoint® PATIENT CARE

MEDICATION (GENERIC)	MEDICATION (BRAND)	INHALER NAME	DEVICE TYPE	TYPICAL FREQUENCY (HOURS)	OPTIMUM INSPIRATORY FLOW RATE FOR CLINICAL EFFECTIVENESS (L/MIN)	MINIMUM REQUIRED INSPIRATORY FLOW RATE FOR EFFECTIVENESS (L/MIN)	FOR LESS THAN MINIMUM REQUIRED FLOW CONSIDER SWITCHING TO:	REF
COMBINATION ICS & LABA								
Budesonide/ Formoterol	Symbicort	HFA	MDI	12	25-60	25	Oral Systemic corticosteroid (prednisone or dexamethasone) AND albuterol nebulized solution (scheduled doses while awake)	1
Fluticasone/ Vilanterol	Breo	Ellipta	DPI	24	60	30		9
Mometasone/ Formoterol	Dulera	HFA	MDI	12	25-60	25		1
Salmeterol/ Fluticasone	Advair	Diskus	DPI	12	60	30		6
	Advair	HFA	MDI	12	25-60	25		1
COMBINATION ICS / LABA / LONG-ACTING ANTICHOLINERGIC								
Fluticasone/ Umeclidinium/ Vilanterol	Trelegy	Ellipta	DPI	24	60	30	Oral systemic corticosteroid (prednisone or dexamethasone) AND ipratropium / albuterol nebulized solution (scheduled doses while awake)	13

"Inhaled Respiratory Medication Chart (Tools for Alternative Therapy)"

Device Type Key

MDI	Metered Dose Inhaler
DPI	Dry Powder Inhaler
NEB	Solution for Nebulization
SMI	Soft Mist Inhaler

References

1. Inhaler Technique and Training in People with Chronic Obstructive Pulmonary Disease and Asthma: Key Issues. Medscape. http://www.medscape.org/viewarticle/757312_11. Accessed November 15th, 2019.
2. Proair Respiclick. [package insert]. Waterford, Ireland: Teva Respiratory, LLC; 2018. http://www.myproair.com/respiclick/library/docs/PI.pdf
3. Foradil Aerolizer. [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2012. https://www.merck.com/product/usa/pi_circulars/f/foradil/foradil_pi.pdf
4. Arcapta Neohaler. [package insert]. Marlborough, MA: Sunovion Pharmaceuticals Inc.; 2019. https://www.arcapta.com/Arcapta-Prescribing-Information.pdf
5. Brand, P., Hederer, B., Austen, G., Dewberry, H., & Meyer, T. (2008). Higher lung deposition with Respimat Soft Mist inhaler than HFA-MDI in COPD patients with poor technique. International journal of chronic obstructive pulmonary disease, 3(4), 763–770.
6. Written communication with the manufacturer. Discussed September 29th, 2015.
7. Tudorza Pressair. [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202450s012lbl.pdf
8. Spiriva Handihaler. [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2018. https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Spiriva/Spiriva.pdf
9. Written communication with the manufacturer. Discussed September 29th, 2015.
10. Pulmicort Flexhaler. [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2008. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021949s003lbl.pdf
11. Asmanex Twisthaler. [package insert]. Whitehouse Station, NJ: Merck & Co. Inc.; 2019. https://www.merck.com/product/usa/pi_circulars/a/asmanex/asmanex_pi.pdf
12. Qvar Redihaler. [package insert]. Waterford, Ireland: Teva Respiratory, LLC; 2018. https://www.qvar.com/globalassets/qvar/qvar-redihaler-pi.pdf
13. Trelegy Ellipta. In: Lexicomp, Lexi-Drugs [database online]. Hudson, OH: Wolters Kluwer Health, Inc; Accessed September 10, 2019.
14. Bevespi Aerosphere [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208294s005lbl.pdf
15. Utibron [package insert]. Marlborough, MA: Sunovion Pharmaceuticals Inc; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207930s004lbl.pdf
16. Yupelri [package insert]. Morgantown, WV: Mylan Specialty LP; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210598s000lbl.pdf
17. Seebri [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207923lbl.pdf
18. Haidl P, Heindl S, Siemon K, Bernacka M, and Cloes RM. Inhalation device requirements for patients' inhalation maneuvers. Resp Med. 2016; 118: 65-75. https://www.resmedjournal.com/article/S0954-6111(16)30160-3/fulltext. Accessed November 1, 2019.

OPIOIDS [A]

OPIOID EQUIANALGESIC CONVERSION TABLE [1*]

OPIOID	ORAL	INJECTABLE	RECTAL	TRANSDERMAL
Buprenorphine	0.4mg (SL)	0.3mg	n/a	**See box A** [2, 3, 4, 5]
Codeine	200mg	120mg (IM only)	200mg [6]	n/a
Fentanyl	**See box B** [7, 8]	0.1mg	n/a	**See box C** [9, 10, 11]
Hydrocodone	30mg	n/a	unknown [33]	n/a
Hydromorphone	7.5mg	1.5mg	3mg [12]	n/a
Levorphanol	4mg	2mg	unknown	n/a
Meperidine	300mg	75mg	300mg [13]	n/a
Methadone	**See box D** [14]	*PO:IV is 2:1* [15]	*PO ≈ PR* [15]	n/a
Morphine	30mg	10mg	30mg [16]	n/a
Oxycodone	20mg	n/a	20mg [17, 18]	n/a
Oxymorphone	10mg	1mg	10mg [12, 19]	n/a
Tapentadol **(See box E)**	100mg [20, 21, 23]	n/a	unknown [22]	n/a
Tramadol **(See box F)**	150 – 300mg [23, 24, 25, 26, 27, 28, 29, 30, 31]	n/a	150 – 300mg [32]	n/a

OPIOID EQUIANALGESIC CONVERSION TABLE[1*]

Box A

Transdermal buprenorphine (TDB)

Converting from another opioid to TDB

The package insert recommends a conservative approach to conversions:

- If total daily Oral Morphine Equivalent (OME) is < 30mg, start at 5mcg/hr patch
- If total daily OME is 30 – 80mg, taper opioid, over a 7 day period, to 30mg OME per day then start 10mcg/hr patch
- If OME > 80mg, TDB may not provide adequate analgesia

It is important to remember that bi-directional equivalency cannot be assumed. Frequent and timely evaluation of all patients undergoing a TDB conversion is strongly advised.

Converting from TDB to another opioid

Conversions that can **potentially** be used bi-directionally have been published and use the total daily mg amount of buprenorphine delivered as a starting point. However, they may not be mathematically consistent across all drugs. For example, the 10mcg/hr patch delivers 240mcg/day or 0.24mg/day. These studies reported ratios of 1mg TDB to 70 – 115mg OME/day. In a "patch to patch" conversion one study reviewed the conversion between transdermal fentanyl (TDF) and TDB and reported a TDF:TDB conversion ratio of 0.6:0.8. For example, 50mcg/hr TDF ≈ 70mcg/hr TDB.

Note: Although higher doses have been used in other countries, the max recommended dose of TDB is one 20mcg/hr patch due to the risk of QTc-interval prolongation.

Box B

Oral fentanyl dosage forms should be reserved for opioid-tolerant patients taking an OME of at least 60mg/day

Other opioid to oral fentanyl:

Attempts at equianalgesic conversion from other opioids to oral fentanyl products is not recommended – always start at the recommended initial dose for each specific product and titrate based on response.

Oral fentanyl to other opioid:

When converting from an oral fentanyl dosage form to a non-fentanyl opioid, an equivalency of 200mcg Actiq : 6-12mg oral morphine has been published. If converting from a dosage form other than Actiq, this conversion should be adjusted for the relative differences in bioavailablities between oral fentanyl products. Approximate biovailabilities are as follows: lozenge (50%), SL tablet (54%), buccal tablet (65%), SL spray (76%). For example, the buccal tablet is 30% more potent (65 – 50 / 50 = 30%) than the lozenge, so a 200mcg buccal tablet is approximately equal to 260mcg Actiq.

Oral fentanyl to a different oral fentanyl:

- To lozenge: always start at 200mcg
- To SL tablet: always start at 100mcg
- To buccal tablet or SL spray: always start at 100mcg, unless converting from lozenge, then:
  lozenge dose 200 – 400mcg 100mcg buccal tablet / SL spray; lozenge dose 600 – 800mcg
  200mcg buccal tablet/SL spray; lozenge dose 1,200 – 1,600mcg buccal tablet / SL spray dose 400mcg
- To buccal film: always start buccal film at 200mcg

Box C

Transdermal Fentanyl (TDF)

24hr Oral Morphine : Transdermal Fentanyl ratio is ≈ 50 – 60mg: 25mcg/hr changed every 72 hours.

OPIOID EQUIANALGESIC CONVERSION TABLE[1*]

Box D

<u>For conversion to oral methadone from other opioids:</u>

Convert the total daily dose (TDD) of all opioids to oral morphine equivalents (OME) first, then calculate the equianalgesic methadone dose based on the total daily OME. The total daily methadone amount is usually divided as BID or TID dosing.

24-hour oral morphine	*Oral morphine : oral methadone conversion ratio*
< 30mg	2 to 1
31 – 99mg	4 to 1
100 – 299mg	8 to 1
300 – 499mg	12 to 1
500 – 999mg	15 to 1
1,000 – 1,200mg	20 to 1
> 1,200mg	expert consult recommended

<u>For conversion from methadone to another opioid:</u>

There is little published evidence to guide this conversion. If recently converted to methadone, consider the using prior opioid regimen rather than the current methadone regimen as the basis for conversion. If this is not possible, a 3:1 oral morphine:oral methadone ratio if likely safe, but the conversion ratio may be higher (eg, 6:1)

Box E

There is limited data to support conversions between tapentadol and pure opioid agonists. Some protocols advise against attempting these conversions. Per the Canadian product labeling, comparable pain relief was observed between tapentadol ER and Oxycontin at a dose ratio of 5:1.

There are different types of pain (eg, nociceptive, visceral, neuropathic). Tapentadol is not indicated for a specific type of pain and it is known to inhibit reuptake of norepinephrine and serotonin (both involved in the potentiation of neuropathic pain). Therefore, adequacy of a calculated equianalgesic dose may vary among individuals based on their unique pain type(s).

Note: maximum daily dose is 500mg/day.

Box F

There is limited data to support conversions between tramadol and pure opioid agonists. Some protocols advise against attempting these conversions. The best available evidence suggests that tramadol is about 10 – 20% as potent as oral morphine.

Additionally, as a prodrug, tramadol requires hepatic conversion to its active form via CYP2D6. There is substantial inter-individual variability of the expression of CYP2D6 (genetic polymorphism). Phenotype variations range from poor metabolizers (tramadol would be minimally potent) to ultrarapid metabolizers (tramadol would be maximally potent).

There are different types of pain (eg, nociceptive, visceral, neuropathic), and tramadol is known to inhibit reuptake of norepinephrine and serotonin (both involved in the potentiation of neuropathic pain). Therefore, adequacy of a calculated equianalgesic dose may vary among individuals based on their unique pain type(s).

Note: maximum daily dose is 400mg/day (300mg/day if age > 75 years; 200mg/day if CrCl < 30ml/min).

Always consider the need to reduce the calculated equivalent dose amount to account for incomplete cross-tolerance. Experts commonly recommend a dose reduction in the range of 25 – 50%.

References

1. UpToDate, Selected opioid analgesics for pain and equianalgesic doses, information current through Dec. 2015.
2. Mercadante, S. et al. Equipotent doses to switch from high doses of opioids to transdermal buprenorphine, Support Care Cancer (2009) 17:715-18.
3. Mercadante, S. et al. Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review, Palliative Medicine, 2011 Vol. 25(5) pp. 504-15.
4. McPherson, ML, 2011 Update to Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing, American Society of Health System Pharmacists, accessed online Dec. 2015 at: http://www.ashp.org/DocLibrary/Bookstore/P1985/2011-Update.aspx
5. Butrans package insert.
6. Moolenaar, F. et al. Rectal versus oral absorption of codeine phosphate in man, Biopharm Drug Dispos, 1983, Vol. 4(2) pp.195-9.
7. Wood, B. Difficult-to-dose Opioids and the Risk Evaluation Mitigation Strategy, US Pharmacist, 2010 Vol. 35(5), pp. 44-50.
8. Lexicomp online database, oral fentanyl monograph, 2015, Lexi-Comp, Inc.
9. McPherson, ML, Demystifying Opioid Conversions - A Guide for Effective Dosing, American Society of Health-System Pharmacists, 2010.
10. Donner, B. et al. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain, Pain, 1996 Vol. 64 pp. 527-34.
11. Breitbart, W. et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain, Oncology, 2000 Vol. 14 pp. 695-705.
12. Drug Facts & Comparisons, 2009, pp. 1139, Walters Kluwer Health.
13. Hamunen, K. et al. Pharmacokinetics of i.v. and rectal pethidine in children undergoing ophthalmic surgery, British Journal of Anaesthesia, 1993 Vol. 71(6) pp. 823-6.
14. Quill, T. et al. Primer of Palliative Care, 2010 ed.
15. Davis, M. et al. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration, Support Care Cancer, 2001 Vol. 9 pp. 73-83.
16. Westerling, D. et al. Absorption and bioavailability of rectally administered morphine in women, European Journal of Clinical Pharmacology, 1982 Vol. 23(1) pp. 59-64.
17. Leow, K. et al. Pharmacokinetics and Pharmacodynamics of Oxycodone When Given Intravenously and Rectally to Adult Patients with Cancer Pain, Anesthesia & Analgesia, 1995 Vol. 80(2) pp. 296-302.
18. Lugo, R. et al. The Pharmacokinetics of Oxycodone, Journal of Pain & Palliative Care Pharmacotherapy, 2004, Vol. 18(4), pp. 17-30.
19. Beaver, W. et al. A comparison of the analgesic effect of oxymorphone by rectal suppository and intramuscular injection in patients with postoperative pain, Journal of Clinical Pharmacology, 1977 Vol. 17(5-6) pp. 276-91.
20. Mercadante, S. et al. Opioid switching from and to tapentadol extended release in cancer patients: conversion ratio with other opioids, Current Medical Research & Opinion, 2013 Vol. 29(6) pp. 661-66.
21. Lexicomp online database, tapentadol monograph, 2015, Lexi-Comp, Inc.
22. Per representative at Depomed Pharmaceutical (866-458-6389), as of Dec. 2015, there is no data available to support rectal use of tapentadol.
23. Veterans Affairs / Department of Defense, VA/DoD Clinical Practice Guideline: Management of Opioid Therapy for Chronic Pain, 2010, accessed online at: http://www.va.gov/painmanagement/docs/cpg_opioidtherapy_summary.pdf
24. Grond, et al. High-Dose Tramadol in Comparison to Low-Dose Morphine for Cancer Pain Relief, Journal of Pain and Symptom Management, 1999, Vol. 18(3) pp. 174-9.
25. Grond, et al. Clinical Pharmacology of Tramadol, Clinical Pharmacokinetics, 2004, Vol. 43(13) pp. 879-923.
26. Wilder-Smith, C. et al. Effects of Morphine and Tramadol on Somatic and Visceral Sensory Function and Gastrointestinal Motility after Abdominal Surgery, Anesthesiology, 1999 Vol. 91(3) pp. 639-47.
27. Allerton, C. et al. Pain Therapeutics - Current and Future Treatment Paradigms, p. 79, Royal Society of Chemistry (RSC) publishing, 2013.
28. Dickman, A. Drugs in Palliative Care, p. 529, Oxford University Press, 2012.
29. Fukuda, K. Miller's Anaesthesia, 8th ed. Chapter: Opioid Analgesics, Elsevier Health Sciences, 2014.
30. Peck, T. et al. Pharmacology for Anaesthesia and Intensive Care, 3rd ed. p. 139, Cambridge University Press, 2008.
31. GlobalRPh.com, Opioid analgesic converter, accessed online Dec. 2015 at: http://www.globalrph.com/narcoticonv.htm
32. Lintz, W. et al. Pharmacokinetics of tramadol and bioavailability of enteral tramadol formulations. 3rd communication: suppositories, Arzneimittelforschung, 1998, Vol. 48(9) pp. 889-99.
33. AbbVie pharmaceuticals, 1800-633-9110, per Kendal, Rph no information to support rectal use of hydrocodone as of Jan. 2016 (case #US15-007748).

BENZODIAZEPINE EQUIVALENCY TABLE [B]

GENERIC NAME	BRAND NAME	AVAILABLE DOSAGE FORMS	APPROXIMATE ORAL EQUIVALENT DAILY DOSE [1, 2]	ONSET OF ACTION *[3]	DURATION OF ACTION (ELIMINATION OF HALF-LIFE) [4]	USUAL ADULT DAILY DOSE (MG)
Alprazolam	Xanax	Solution, Tablet	0.5mg	Intermediate	Intermediate (8 – 12 hours)	0.5 – 4
Chlordiazepoxide	Librium	Capsule	25mg	Intermediate	Long (24 – 48 hours)	15 – 100
Clonazepam	Klonopin	Tablet	0.5mg	Intermediate	Long (18 – 60 hours)	1.5 – 20
Clobazam	Onfi	Tablet; Suspension	20mg	Rapid	Long (36 – 42 hours)	20 – 80
Clorazepate	Tranxene T-Tab	Capsule; Tablet	15mg	Slow	Long (40 – 50 hours)	15 – 60
Diazepam	Valium	Gel; Injection; Solution; Tablet	10mg	Rapid	Long (14 – 100 hours)	4 – 40
Estazolam	Pro-Som	Tablet	1 – 2mg	Slow	Intermediate (10 – 24 hours)	1 – 2
Flurazepam	Dalmane	Capsule	15 – 30mg	Rapid	Long (47 – 100 hours)	15 – 60
Lorazepam	Ativan	Injection; Solution; Tablet	1 – 2mg	Intermediate	Intermediate (8 – 24 hours)	2 – 4
Midazolam	Versed	Injection	N/A	Very Rapid	Very Short (2 hours)	N/A
Oxazepam	Serax	Capsule; Tablet	20mg	Slow	Short (5 – 14 hours)	30 – 120
Temazepam	Restoril	Capsule	30mg	Slow	Intermediate (8 – 22 hours)	7.5 – 30
Triazolam	Halcion	Tablet	0.5mg	Intermediate	Short (1.5 – 5 hours)	0.125 – 0.25

*Onset of action: rapid= within 15 minutes; Intermediate= 15 – 30 minutes; Slow= 30 – 60 minutes

References

1. C Heather Ashton, DM, FRCP. Benzodiazepine Equivalency Table. Available at http://www.bcnc.org.uk/equivalence.html
2. Clincalc.com. Equivalent Benzodiazepine Calculator, 2014
3. Available at: http://www.vhpharmsci.com/vhformulary/tools/benzodiazepines-comparison.htm. Accessed June 24, 2015
4. Lexicomp Online. Copyright © 1978-2015 Lexicomp, Inc. All Rights Reserved

SSRI AND SNRI ANTIDEPRESSANT CHART[D]

	GENERIC NAME	BRAND NAME	AVAILABLE DOSAGE FORMS	USUAL DAILY STARTING DOSE	USUAL DAILY DOSAGE RANGE	MAX DOSE
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)[a]	Citalopram[a]	Celexa	Tablet; Solution	20mg	20 – 40mg	40mg
	Escitalopram[a]	Lexapro	Tablet; Solution	10mg	10 – 20mg	20mg
	Fluoxetine	Prozac[a]	Capsule; Tablet; Solution	20mg	20 – 80mg	80mg
		Prozac Weekly[b]	Delayed-Release Capsule	90mg/week	90mg/week	90mg/week
	Paroxetine[a]	Paxil	Tablet; Suspension	20mg	10 – 50mg	60mg
		Paxil CR	Extended-release Tablet	25mg	25 – 62.5mg	62.5mg
	Sertraline[a]	Zoloft	Tablet; Solution	50mg	50 – 200mg	200mg
SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR (SNRI)	Desvenlafaxine[a]	Prestiq	Extended-release tablet	50mg	50 – 100mg	100mg
	Duloxetine[d]	Cymbalta	Delayed-release capsule	30 – 60mg	30 – 120mg	120mg
	Levomilnacipran[a]	Fetzima	Extended-release capsule	20mg	40 – 120mg	120mg
	Venlafaxine	Effexor[c]	Tablet	37.5 – 75mg	73 – 375mg	375mg
		Effexor Xra	Extended-release capsule; Extended-release tablet	37.5 – 75mg	75 – 225mg	225mg

NOTES:

- Cross tapering is recommended by gradually reducing the current antidepressant dose while gradually increasing the new antidepressant over 1-2 weeks or longer to minimize drug withdrawal effects.[2]

a. Generally dosed once daily

b. Dosed once weekly

c. Generally dosed once daily

d. Generally dosed once to twice daily

References

1. Lexicomp Online. Copyright © 1978-2015 Lexicomp, Inc. All Rights Reserved.

2. Hirsch M, Birnbaum R. Antidepressant Medication in Adults: Switching and Discontinuing Medication. UpToDate. 2015 Aug. Available at: http://www.uptodate.com/contents/antidepressant-medication-in-adults-switching-and-discontinuing-medication

ANTIPSYCHOTIC EQUIVALENCY CHART[F]

	GENERIC NAME	BRAND NAME	AVAILABLE DOSAGE FORMS	APPROXIMATE EQUIVALENT ORAL DOSAGES (MG/DAY)[1, 2]	USUAL ADULT DAILY MAINTENANCE DOSE (MG)[3]
ATYPICAL ANTIPSYCHOTICS	Aripiprazole	Abilify	Tablet; Injection; Solution; Orally disintegrating tablet	7.5mg	10 – 30mg
		Abilify Maintena	Long-acting injection	Not available	160 – 400mg monthly*
	Asenapine	Saphris	Saphris	5mg	10 – 20mg
	Clozapine	Clozaril	Tablet; Orally disintegrating tablet	100mg	75 – 900mg
	Iloperidone	Fanapt	Tablet	6mg	12 – 24mg
	Lurasidone	Latuda	Tablet	20mg	20 – 160mg
	Olanzapine	Zyprexa	Tablet; Injection; Orally disintegrating tablet	5mg	5 – 20mg
		Zyprexa Relprevv	Long-acting injection	Not available	150 – 405mg every 2 – 4 weeks*
	Paliperidone	Invega	Extended Release Tablets	1.5mg	6 – 12mg
	Quetiapine	Seroquel, Seroquel XR	Tablet; Extended release tablet	75mg	50 – 800mg
	Risperidone	Risperdal	Tablet, Solution; Orally disintegrating tablet	2mg	0.5 – 6mg
		Risperdal Consta	Long-acting injection	25mg per 14 days	25 – 50mg every 2 – 4 weeks*
	Ziprasidone	Geodon	Capsule	7.5mg	40 – 160
TYPICAL ANTIPSYCHOTICS	Chlorpromazine	Thorazine	Tablet; Injection	100mg	200 – 1000mg
	Fluphenazine	Prolixin	Tablet; Solution; Injection	2mg	0.5 – 20mg
	Haloperidol	Haldol	Tablet; Solution; Injection	2mg	0.5 – 20mg
		Haldol Decanoate	Long-acting injection	30mg per 28 days	50 – 200mg monthly*
	Loxapine	Loxitane	Capsule	10mg	10 – 80mg
	Perphenazine	Trilafon	Tablet	8mg	10 – 64mg
	Thioridazine	Mellaril	Tablet	100mg	100 – 800mg
	Thiothixene	Navane	Capsule	4mg	4 – 40mg
	Trifluoperazine	Stelazine	Tablet	2mg	5 – 40mg

*Consult drug monograph for specific dosage details.

References

1. Danivas V, Venkatasubramanian G. Current perspectives on chlorpromazine equivalents: Comparing apples and oranges!. Indian J Psychiatry. 2013;55(2):207-8.
2. Woods SW. Chlorpromazine equivalent doses for the newer atypical
3. Lexicomp Online. Copyright © 1978-2015 Lexicomp, Inc. All Rights Reserved.

LOOP DIURETICS [H]

GENERIC NAME	BRAND NAME	AVAILABLE DOSAGE FORMS	APPROXIMATE EQUIVALENT ORAL DOSAGE (MG) [1, 2]	USUAL ADULT DAILY DOSE (MG) [3]	DURATION OF ACTION (HOURS) [1, 3]
Bumetanide	Bumex	Tablet; IV	1	0.5 – 2	4 – 6
Furosemide	Lasix	Tablet; Oral solution; IV	40	20 – 320	6
Torsemide	Demadex	Tablet	20	5 – 100	6 – 12

References

1. Anaizi N. Diuretics. The Drug Monitor. 2011. Available at: http://www.thedrugmonitor.com/diuretics.html
2. Abel EE, Folse SL, et al. Loop Diuretic Therapy. Society of Critical Care Medicine. 2012 Nov 15. Available at: http://www.learnicu.org/Lists/Web%20Contents/
3. Loop Diuretics. LiverTox. 2015 Aug 31. Available at: http://livertox.nih.gov/LoopDiuretics.htm

Medication Conversions

SYSTEMIC CORTICOSTEROIDS[1]

GENERIC NAME	BRAND NAME	AVAILABLE DOSAGE FORMS	APPROXIMATE EQUIVALENT ORAL DOSAGE (MG)[1,2]	POTENCY
Dexamethasone	Decadron	Tablet; Solution; Injection	0.75	Most potent
Methylprednisolone	Solu-Medrol	Tablet; Injection	4	
Prednisone	Deltasone	Tablet; Solution	5	
Prednisolone	Pediapred; OraPred	Tablet; Solution; Orally disintegrating tablet	5	
Hydrocortisone	Solu-Cortef	Tablet	20	
Cortisone	Cortone	Tablet	25	Least potent

References

1. Corticosteroids Systemic Equivalencies. Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.1978-2013 [accessed 2015 Sep 14]. Available from: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/4144
2. Using Oral Corticosteroid: a Toolbox. Pharmacist's Letter/Prescriber's Letter 2010; 26(5):26507.

PROTON PUMP INHIBITORS [J]

GENERIC NAME	BRAND NAME	GENERIC AVAILABLE	OTC AVAILABLE	AVAILABLE DOSAGE FORMS [1]	APPROXIMATE EQUIVALENT ORAL DOSAGE (MG) [2]	USUAL ADULT DAILY DOSE (MG) [3, a]
Dexlansoprazole	Kapidex	No	No	Capsule	60mg	30 – 60mg
Esomeprazole	Nexium	No	Yes	Capsule; Packet; IV	20 – 40mg	20 – 40mg
Lansoprazole	Prevacid	Yes	Yes	Capsule; Suspension, ODT	30mg	15 – 30mg
Omeprazole	Prilosec	Yes	Yes	Capsule; Packet; Suspension; Tablet	20mg	20 – 40mg
Pantoprazole	Protonix	Yes	No	Packet; IV; Tablet	40mg	40mg
Rabeprazole	Aciphex	Yes	No	Capsule sprinkle; Tablet	20mg	20 – 40mg

a. Usual dose for all indications except pathological hypersecretory conditions, which requires much higher dosing

References

1. Lexicomp Online. Copyright © 1978 - 2015 Lexicomp, Inc. All Right Reserved.
2. Proton Pump Inhibitor Dosage Comparison Chart. Pharmacist's Letter, 2009; 25(8):250831
3. "Proton Pump Inhibitors: U.S.F.D.A.-Approved Indications and Dosages for Use in Adults". Fact Sheet. Center for Medicaid and Medicare Services.August 2013. Web. Available at: https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/Downloads/ppi-adult-dosingchart.pdf

THYROID HORMONE REPLACEMENT EQUIVALENCE[K]

DRUG	NP THYROID (THYROID USP)	WP THYROID (THYROID USP)	NATURE-THROID (THYROID USP)	ARMOUR THYROID (THYROID USP)	SYNTHROID / LEVOXYL (LEVOTHYROXINE SODIUM)	TIROSINT (LEVOTHYROXINE SODIUM)
HORMONE TYPE	T_3/T_4	T_3/T_4	T_3/T_4	T_3/T_4	T_4	T_4
APPROXIMATE EQUIVALENT DOSE						0.013mg (13mcg)
	15mg (1/4 grain)	16.25mg (1/4 grain)	16.25mg (1/4 grain)	15mg (1/4 grain)	0.025mg (25mcg)	0.025mg (25mcg)
	30mg (1/2 grain)	32.5mg (1/2 grain)	32.5mg (1/2 grain)	30mg (1/2 grain)	0.05mg (50mcg)	0.05mg (50mcg)
	45mg (3/4 grain)	48.75mg (3/4 grain)	48.75mg (3/4 grain)		0.075mg (75mcg)	0.075mg (75mcg)
					0.088mg (88mcg)	0.088mg (88mcg)
	60mg (1 grain)	65mg (1 grain)	65mg (1 grain)	60mg (1 grain)	0.1mg (100mcg)	0.1mg (100mcg)
					0.112mg (112mcg)	0.112mg (112mcg)
	75mg (1.25 grain)	81.25mg (1.25 grain)	81.25mg (1.25 grain)		0.125mg (125mcg)	0.125mg (125mcg)
					0.137mg (137mcg)	0.137mg (137mcg)
	90mg (1.5 grain)	97.5mg (1.5 grain)	97.5mg (1.5 grain)	90mg (1.5 grain)	0.150mg (150mcg)	0.150mg (150mcg)
	105mg (1.75 grain)	113.75mg (1.75 grain)	113.75mg (1.75 grain)		0.175mg (175mcg)	
	120mg (2 grain)	130mg (2 grain)	130mg (2 grain)	120mg (2 grain)	0.2mg (200mcg)	
	135mg (2.25 grain)		146.25mg (2.25 grain)			
	150mg (2.5 grain)		162.5mg (2.5 grain)			
	180mg (3 grain)		195mg (3 grain)	180mg (3 grain)	0.3mg (300mcg) Synthroid Only	
			280mg (4 grain)	240mg (4 grain)		

Note: all entries are approximate equivalencies based off of USP Drug Information 20th Edition conversion (1 grain (60mg) T3/4 = 100mcg T4) and manufacturer data

References

1. Ross DS, et al. Treatment of primary hypothyroidism in adults. UptoDate. Accessed May 8, 2019.
2. RLC Labs. https://getrealthyroid.com/conversion-guide.html
3. Acella Pharmaceuticals. http://npthyroid.com/wp-content/uploads/2017/12/Naturethroid_Conversion_Chart.pdf

OPIOID SELECTION WITH RENAL IMPAIRMENT

EFFECTS OF CKD AND RENAL FAILURE (RF) ON OPIOID PHARMACOKINETICS

OPIOID	ORAL ABSORPTION	DISTRIBUTION	METABOLISM	EXCRETION	CLINICAL SIGNIFICANCE
Buprenorphine	Normal: N/A (SL: 50%) RF: unknown effect	Normal: 96% bound to alpha/beta globulin RF: unknown effect	Phase I: CYP3A4 to active metabolite Phase II: glucoronidation RF: unknown effect on Phase I; Phase II preserved	Normal: biliary / fecally (70%) and renally (30%) as glucuronides RF: unknown	Has not been adequately studied in patients not receiving dialysis --> CAUTION One study of dialysis patients found no changes. --> SAFE
Codeine	Normal: 53% RF: unknown effect	Normal: 7-25% bound to albumin RF: unknown effect	Phase I: CYP2D6/3A4 to active metabolite (morphine) Phase II: glucuronidation of morphine to M3G & M6G RF: Unknown effect	Normal: renally (10% as codeine; 90% as metabolites) RF: clearance reduced; even trivial doses have resulted in clinically significant AE	Due to the high likelihood of clinically relevant adverse effects, alternate therapy is recommended with any level of renal impairment --> AVOID
Fentanyl	Normal: N/A (SL/ transmucosal 50-76%) RF: unknown effect	Normal: 79-87% bound mainly to alpha-1-acid glycoprotein and albumin to a lesser extent RF: unknown effect	Phase I: CYP3A4 to inactive metabolites RF: unknown effect	Normal: renally as inactive metabolites RF: parent may accumulate in severe renal failure	Although sometimes considered a drug of choice for this population, consider empiric dose reduction of 25-50% when starting or converting to fentanyl --> SAFE
Hydromorphone	Normal: 24% RF: unknown effect	Normal: 8-19% bound RF: unknown effect	Phase II: glucuronidation mostly to H3G (inactive/ neurotoxic) RF: no effect	Normal: renally primarily as glucuronide metabolites RF: H3G can accumulate potentially causing adverse effects/ neurotoxicity	Safer than morphine / considered a drug of choice; use reduced initial dose; adverse effects due to H3G accumulation are related to dose (more than 20mg/hr parenterally) and duration of use (longer than 15 days) --> CAUTION
Methadone	Normal: 36-100% RF: unknown effect	Normal: 85-90% bound primarily to alpha-1-acid glycoprotein RF: unknown effect	Phase I: CYP3A4/2B6/2C19 to inactive metabolites RF: unknown effect	Normal: renally and biliary/ fecally RF: reduced renal excretion overcome by increased biliary/ fecal excretion	Does not accumulate in RF --> SAFE
Morphine	Normal: 20-40% RF: unknown effect	Normal: 20-35% bound RF: unknown effect	Phase II: glucuronidation to M3G (neurotoxic) and M6G (active) RF: no effect	Normal: renally as glucuronide metabolites RF: metabolites accumulate potentially causing adverse effects/ neurotoxicity	Avoid prolonged use in patients with RF; if using, monitor for symptoms of opioid induced neurotoxicity / myoclonus --> AVOID
Oxycodone	Normal: 60-87% RF: unknown effect	Normal: 45% bound RF: unknown effect	Phase I: CYP2D6/3A4 to active and inactive metabolites RF: unknown effect	Normal: renally as parent and metabolites RF: parent and metabolites accumulate	Considered to be safer than morphine in patients with RF; half-life may be increased / consider extended interval dosing; serum concentrations increased by ~50%; adjust based on clinical situation --> CAUTION
Tramadol	Normal: IR: 75%; ER: 85-90% RF: unknown effect	Normal: 20% bound RF: unknown effect	Phase I: CYP3A4/2B6 to active metabolite (parent inactive) Phase II: glucuronidation, sulfation RF: unknown effect	Normal: Renally 30% as parent; 70% as metabolites RF: parent and metabolites accumulate	IR form: to prevent adverse effects due to accumulation, extend dosing interval to Q12 hours (max 200mg/day) --> CAUTION ER form: contraindicated

A "LXIII. Medication Adjustment in Renal or Hepatic Impairment"

OPIOID SELECTION WITH HEPATIC IMPAIRMENT

EFFECTS OF HEPATIC FAILURE (HF) ON OPIOID PHARMACOKINETICS

OPIOID	ORAL ABSORPTION	DISTRIBUTION	METABOLISM	EXCRETION	CLINICAL SIGNIFICANCE
Buprenorphine	Normal: N/A (SL: 50%) HF: unchanged	Normal: 96% bound to alpha/beta globulin HF: increased free drug	Phase I: CYP3A4 to active metabolite Phase II: glucoronidation HF: unknown, but likely reduced	Normal: biliary / fecally (70%) and renally (30%) as glucuronides HF: unknown, but likely reduced	Unknown, but decreased metabolism and excretion are likely resulting in accumulation and increased duration of action --> AVOID
Codeine	Normal: 53% HF: clinically insignificant changes	Normal: 7-25% bound to albumin HF: clinically insignificant changes	Phase I: CYP2D6/3A4 to active metabolite (morphine) Phase II: glucuronidation of morphine to M3G & M6G HF: reduced	Normal: renally (10% as codeine; 90% as metabolites) HF: not affected	Reduced conversion to active form (morphine) known to occur, resulting in reduced/ inadequate analgesia --> AVOID
Fentanyl	Normal: N/A (SL/ transmucosal 50-76%) HF: unchanged	Normal: 79-87% bound mainly to alpha-1-acid glycoprotein and albumin to a lesser extent HF: increased free drug / volume of distribution	Phase I: CYP3A4 to inactive metabolites HF: reduced	Normal: renally as inactive metabolites HF: not affected	Concentration and half-life increased; consider empiric dose reduction of 50% when initiating or converting to fentanyl --> CAUTION
Hydromorphone	Normal: 24% HF: increased if portal-systemic shunt	Normal: 8-19% bound HF: clinically insignificant changes	Phase II: glucuronidation mostly to H3G (inactive/ neurotoxic) HF: metabolism preserved until severe HF	Normal: renally primarily as glucuronide metabolites HF: not affected	Consider empiric reduction of 50% if portal-systemic shunt; likely longer duration of action so consider extended interval dosing --> CAUTION
Methadone	Normal: 36-100% HF: clinically insignificant changes	Normal: 85-90% bound primarily to alpha-1-acid glycoprotein HF: increased free drug / volume of distribution	Phase I: CYP3A4/2B6/2C19 to inactive metabolites HF: reduced	Normal: renally and biliary / fecally HF: clinically insignificant changes in biliary / fecal excretion	Despite predicted increase in potency due to reduced protein binding and metabolism, studies indicate no dose adjustment needed, potentially due to reduced ability of the liver to store and release methadone --> CAUTION
Morphine	Normal: 20-40% HF: increased if portal-systemic shunt	Normal: 20-35% bound HF: clinically insignificant changes	Phase II: glucuronidation to M3G (neurotoxic) and M6G (active) HF: metabolism preserved until severe HF	Normal: renally as glucuronide metabolites HF: not affected	Consider empiric reduction of 50% if portal-systemic shunt; likely longer duration of action so consider extended interval dosing --> CAUTION
Oxycodone	Normal: 60-87% HF: clinically insignificant changes	Normal: 45% bound HF: clinically insignificant changes	Phase I: CYP2D6/3A4 to active and inactive metabolites HF: reduced leading to half-life increase of ~2.3 hours	Normal: renally as parent and metabolites HF: not affected	Due to reduced metabolism, lower doses or longer intervals should be considered --> CAUTION
Tramadol	Normal: IR: 75%; ER: 85-90% HF: clinically insignificant changes	Normal: 20% bound HF: clinically insignificant changes	Phase I: CYP3A4/2B6 to active metabolite (parent inactive) Phase II: glucuronidation, sulfation HF: reduced	Normal: Renally 30% as parent; 70% as metabolites HF: increased % excreted as parent	Reduced conversion to active form known to occur, resulting in reduced / inadequate analgesia --> AVOID

B "LXIII. Medication Adjustment in Renal or Hepatic Impairment"

ANTIBIOTIC SELECTION WITH RENAL IMPAIRMENT

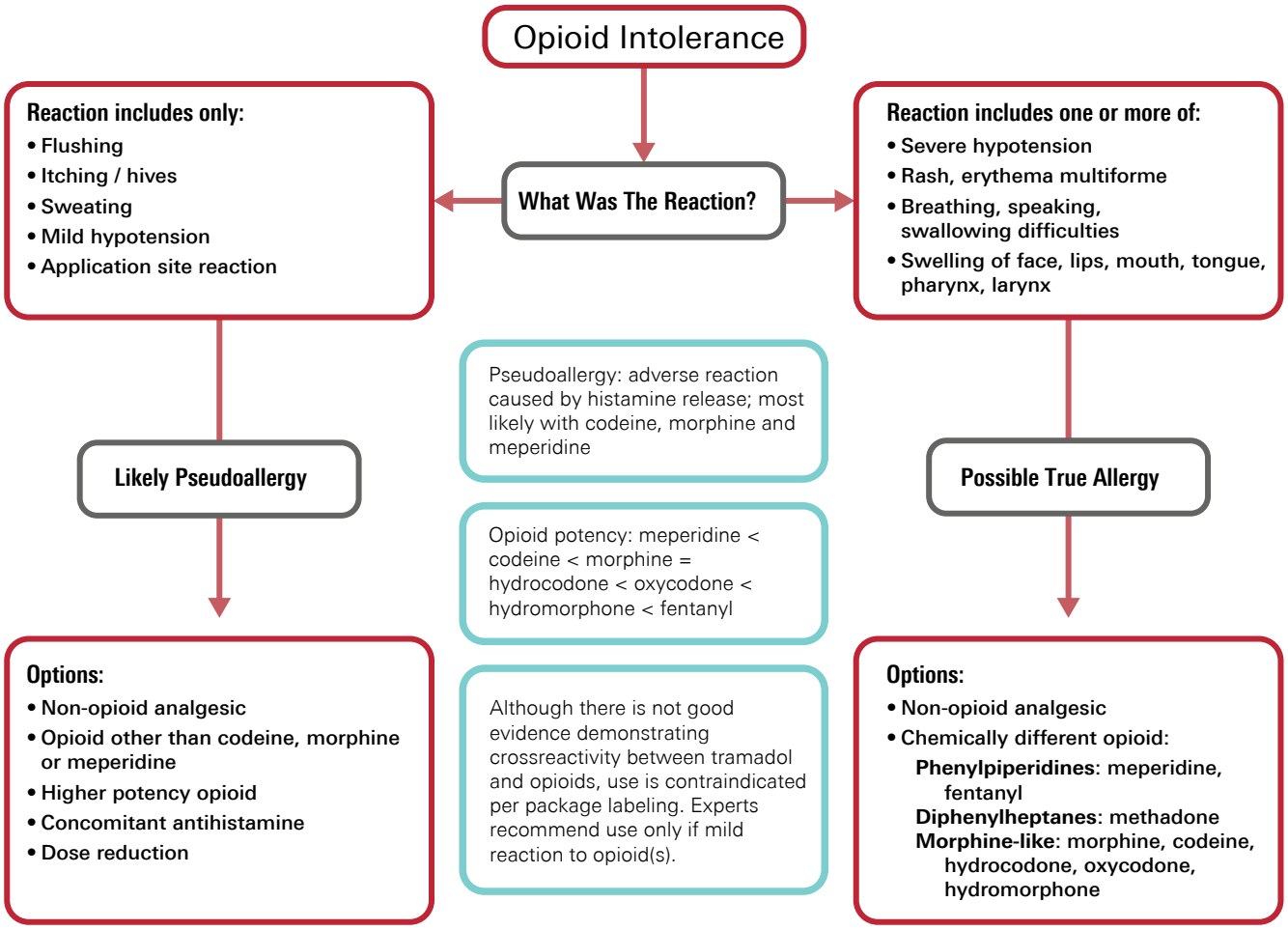
RECOMMENDED RENAL DOSING ADJUSTMENT FOR COMMONLY USED ANTIBIOTICS

Antibiotic(s)	CrCl (ml/min)	Suggested Dosing Adjustment
Amoxicillin (Amoxil), amoxicillin/clavulanate (Augmentin)	10-30	250 – 500mg Q12 hours
	< 10	250 – 500mg Q24 hours
Azithromycin (Zithromax)	-	No adjustment recommended
Cephalexin (Keflex)	10-50	250 – 500mg Q8-12 hours
	< 10	250 – 500mg Q12-24 hours
Ciprofloxacin (Cipro)	30-50	250 – 500mg Q12hours
	5-29	250 – 500mg Q18 hours
Doxycycline (Vibramycin)	-	No adjustment recommended
Levofloxacin (Levaquin)	20-49	If 750mg QD w/o adjustment: 750mg Q48 hours
		If 500mg QD w/o adjustment: 500mg x 1 dose, then 250mg Q24 hours
	10-19	If 750mg QD w/o adjustment: 750mg x 1 dose, then 500mg Q48 hours
		If 500mg QD w/o adjustment: 500mg x 1 dose, then 250mg Q48 hours
		If 250mg QD w/o adjustment: 250mg Q48 hours
Metronidazole (Flagyl)	< 10	Recommendations vary: reduce dose by 50% or give Q12 hours
Nitrofurantoin (Macrobid, Macrodantin)	< 60	Contraindicated
Sulfamethoxazole/Trimethoprim (Bactrim)	15-30	Reduce dose by 50%
	< 15	Not recommended

References

1. Lexicomp
2. Kapur, B. et al. Methadone: a review of drug-drug and pathophysiological interactions, Critical Reviews in Clinical laboratory Sciences, 200;48(4):171-95.
3. Prommer, E. et al. Retrospective study of adverse effects in patient with renal failure recieivng hydromorphone, 2011 AAHPM & HPNA annual assembly.
4. Hartman, A. Opioid selection and dosing in hepatic and renal failure, 2011 AAHPM & HPNA annual assembly.

OPIOID ALLERGY/INTOLERANCE DECISION ALGORITHM [A]



GLUTEN FREE MEDICATION CONSIDERATIONS[B]

Patients with Celiac Disease should avoid foods with gluten. Those who strictly adhere to their diet and have a severe allergy to gluten may require avoiding medications that may have gluten contents. Trace presence of gluten (food contamination or medications) can be safe for many patients. If a patient is requesting gluten free medications verify the patient has a documented history of Celiac Disease and follows a strict gluten free diet. For patients who do not follow a strict diet, avoiding medications with gluten may not be necessary.

Manufactures use fillers or excipients to produce medications which may have products that should be avoided. Manufactures use different excipients, looking up the each medication individually is advised. Listed below are some basics when looking for medications that are gluten free. Information about the inactive ingredients can be looked up in the manufacture's package insert or on the website http://dailymed.nlm.nih.gov/dailymed/ (be aware of the manufacture when researching).

Ingredients that would indicate Gluten-Free:

- Cornstarch or starch (corn)
- Dextran and dextrose

Ingredients that would trigger either further clarification or avoidance

- Wheat
- Starch or modified starch can be derived from many sources
- Dextrate and dextrin can be derived from many sources
- Caramel coloring (when barley malt is used)

Please visit this site for a complete list of medications glutenfreedrugs.com. Keep in mind that the list may not be the most updated.

References

1. Adapted from: Pharmacist's Letter Detail-Document #220201 Opioid Intolerance Decision Algorithm, 2010.
2. Information gathered from http://www.celiaccentral.org/gluteninmeds/

OPIOID AND BENZODIAZEPINE KINETICS TABLES

OPIOIDS

DRUG NAME	ROUTE	ONSET (MIN)	TIME TO PEAK (MIN)	DURATION OF ACTION (HOURS)	TIME TO STEADY STATE (HOURS)	HALF-LIFE (HOURS)
Buprenorphine	Buccal (Belbuca)	30-60[59]	150-180	No data found (dosed Q12h)	~60[64]	16.4-38.8
	SQ implant (Probuphine)	No data found	720	4,032	~672	24-48
	Transdermal (Butrans)	660-1,260 (dose-dependent)	3,600	72-168 (dose-dependent)	72	26
	IV	60	15-180[60]	2-24	8.8-15	1.2-7.2
	IM	15	60 (analgesic effect)	≥6	No data found	No data found
	SQ injection (Sublocade)	No data found	1,400	No data found	2,880-4,320	1,032-1,440
	SL (tablet)	30-60[58]	30-60	6-72[58]	124-175	31-35
Codeine Sulfate	PO	30-60	60-90	4-6	12-15	3
Fentanyl	Buccal (Fentora, Onsolis)	10[15]	20-240 (median: 47)	1-2[16]	28.6-35.75	2.6-11.7
	Intranasal (Lazanda)	Rapid onset[54]	15-21	0.5-1[54]	80-100	15-25
	Transmucosal (Actiq)	5-15	20-40	1-2	15-18.75	1.5-6 (dose dependent)
	Sublingual (Abstral, Subsys)	~8.7-12.7[4, 17, 18]	10-120 (median: 90)	2[4]	34-42.5	5-12
	Transdermal (Duragesic)	360	1,728-2,148	72-96	94-117.5	20-27
	IV	immediate	30-60	0.5-1	12-15	2-4
	SQ	5-15[19]	10-30[20]	0.5-2[21]	40-50	10[20]
Hydrocodone (IR: as hydrocodone/APAP)	PO	10-20	60-96	4-8	15.4-19.25	3.3-4.4
	PO (ER: Zohydro 12-hr)	No data found	~300	24[61]	72	8
	PO (ER: Hysingla 24-hr)	No data found	360-1,800	12[61]	72	7-9
REFERENCES	Book	Calculated from Half-Life	Drugs Facts & Comparisons[50]	Drugs.com[51]	PDR/FDA[52]	Lexicomp[53]
	Manufacturer's website(s)	Medscape[55]	Micromedex[56]	NIH – U.S. Library of Medicine	PubMed	Uptodate[57]

OPIOIDS

DRUG NAME	ROUTE	ONSET (MIN)	TIME TO PEAK (MIN)	DURATION OF ACTION (HOURS)	TIME TO STEADY STATE (HOURS)	HALF-LIFE (HOURS)
Hydromorphone	PO (IR)	15-30	30-60	3-4	10-12.5	2-3
	PO (ER)	360	720-960	13	44-55	11
	SL	Ionized and low lipophilicity via SL route [12]				
	SQ	15	30-90	4 [13]	24 [14]	2.6 [14]
	IV	5	10-20	3-4	9.2-11.5	2.3
	PR	15-30	60 [10]	4-6 [10]	15.2-19	3.8 [12]
Oxycodone	PO (IR)	10-15	90-114	3-6	18-24	2-4
	PO (ER)	60 [22]	162-192 [22]	12 [22]	24-36 [22]	6.9 [22]
	SL	Fast onset [23]	20 [23]	~2.9 [24]	10-12.5	2.5 [24]
	PR	30-60 [25]	168 [11]	8-12 [25]	21.6-27	5.4 [26]
Oxymorphone	PO (IR)	30 [29]	60 [29]	4-6 [29]	72 [29]	7.25-9.43
	PO (ER)	~30 [16]	120 [30]	12 [29]	40-50	9-11
	PR	15-30 [11]	60-90	3-6 [31, 32]	6-7.5	1-2 [31]
Methadone	PO	30-60	60-450	4-8	134-167.5	8-59
	IV	10-20	60-120	4-8	72-120	24-38.4
	PR	15-30 [33]	54-108 [33]	8 [33]	132-165	31-35 [33]
Morphine	PO (IR)	~30	60	3-5	24	1.5-4.5
	PO (ER)	30-90 [1]	30 (Avinza) 516 (Kadian)	>24 (Avinza) [2] 8-24 (Kadian) [3]	48-72	24 (Avinza) 11-13 (Kadian)
	SL	Very slow [4]	105 [4]	5.4 [4]	Very poor absorption via SL route [5]	
	SQ	10-30	50-90	4-5	8.4-10.5	1.7-2.5 [6]
	IV	5-10	20	4-5	12-15	1.5-4.5
	PR	20-60 [7]	43-75 [8, 9]	4-5 [7, 10]	10-12.5	2.2 [11]
Tramadol	PO	60	120	Single dose: 4-6 Multiple dose: 3-11	28-35	6-8
	PR	No data found	198 [27]	8.6 [28]	22.8-28.5	4.7-6.7 [27]
REFERENCES	Book	Calculated from Half-Life	Drugs Facts & Comparisons [50]	Drugs.com [51]	PDR/FDA [52]	Lexicomp [53]
	Manufacturer's website(s)	Medscape [55]	Micromedex [56]	NIH – U.S. Library of Medicine	PubMed	Uptodate [57]

BENZODIAZEPINES

DRUG NAME	ROUTE	ONSET (MIN)	TIME TO PEAK (MIN)	DURATION OF ACTION (HOURS)	TIME TO STEADY STATE (HOURS)	HALF-LIFE (HOURS)
Alprazolam	PO	60-90	60-120	Determined by distribution	44-55	11
Clonazepam	PO (incl. ODT)	20-40	60-240	≤12	72-240	17-60
Diazepam	PO	15[36]	30-90	3-30[36]	180-225	44-48
	SL	No data found				
	IV	1-5[42]	1	0.25-1 (sedation)	156-195	33-45
	SQ	Not used – may cause tissue necrosis[43, 44]				
	PR (gel)	15[45]	108[45]	30[45]	184-230	46
Lorazepam	PO	60	120	up to 8	56-70	12
	SL	5[34]	60	up to 8	72[35]	8[35]
	SQ	Rapid onset	60-90[36]	~8	54-67.5	12-15[36]
	IV	1-3	60-90[37]	6-8	56-70	14
	PR	5[38, 39]	68[39]	6-8[40]	No data found	No data found
Midazolam	PO	10-20	30-60 (sedation)	1-6	18-22.5	2-7
	SL/ buccal	15[36]	30[36]	4[36]	14-17.5	2-5[36]
	IV	3-5	30-60 (sedation)	1-2[45]	16.4-20.5	1.8-6.4
	SQ	5-10[46]	30[36]	4[36]	14-17.5	2-5[36]
	PR	7.5[47]	30[48]	2[47]	12-15	3[49]
Temazepam	PO	30-60	72-96	6 to 10[63]	No data found	3.5-18.4
REFERENCES	Book	Calculated from Half-Life	Drugs Facts & Comparisons[50]	Drugs.com[51]	PDR/FDA[52]	Lexicomp[53]
	Manufacturer's website(s)	Medscape[55]	Micromedex[56]	NIH – U.S. Library of Medicine	PubMed	Uptodate[57]

MEDICATIONS THAT PROLONG THE QTC INTERVAL

In the heart's electrical cycle, QT interval represents depolarization and repolarization of the ventricles. If there is a prolonged interval, it is known as QT interval prolongation or abnormal or delayed ventricular repolarization. When this occurs, there is a risk of causing a condition called torsades de pointes (TdP), which can lead to ventricular fibrillation and sudden death. TdP can be due to congenital or acquired long QT syndrome. Congenital would mean a genetic mutation that increases the risk of long QT syndrome and acquired means that a number of risk factors could increase the risk such as medications, bradycardia, hypokalemia, heart failure, or left ventricular hypertrophy. In the presence of these risk factors, if a patient has new onset syncope, palpitations, seizures, or cardiac arrest, it may be due to QT prolongation and/or TdP.

There are many medications that have documented evidence to cause QT prolongation. The medication could individually cause the prolongation or the medication(s) could alter the metabolism of other medication(s) that could cause the prolongation. Regardless, it is important to be aware of these drug interactions before starting a patient on medications especially if the patient has concomitant risk factors such as female gender, age over 65, bradycardia, hypokalemia, hypomagnesemia, underlying heart disease, prolonged baseline QT, or congenital long QT syndrome. Patients with decreased renal or hepatic dysfunction are also at risk due to reductions in metabolism and elimination of medications. Because of this, adjusting doses for renal and hepatic dysfunction is also important to minimize risk.

The table below is a list of common medications that could cause QT prolongation. Medications in each subcategory separated as a guide to help determine how to manage the interaction. As always, evaluating the medication (dose/frequency), drug-drug interaction, drug-disease interaction, other risk factors, and benefits vs risk should be consider prior to making a decision on continuation of the medication.

If the patient has Congenital Long QT Syndrome there are recommendations to avoid the following medications: albuterol, amphetamine, arformoterol, dobutamine, dopamine, formoterol, levalbuterol, metaproterenol, methylphenidate, midodrine, phenylephrine, pseudoephedrine, salmeterol, and TMP-SMX.

COMMON MEDICATIONS THAT PROLONG QT*

SEVERITY	MEDICATIONS				
Highest Risk of QTc Prolonging Agents	**Amiodarone** **Citalopram*** **Disopyramide** **Dofetilide**	**Dronedarone** **Escitalopram** Fluoxetine	Iloperidone Paliperidone Quetiapine	**Quinidine** Quinine **Sotalol**	Terfenadine Ziprasidone
	*Citalopram risk with doses >40mg and >20mg in patients with hepatic impairment, age >60 years, drug interactions that may increase plasma concentration				
Moderate Risk of QTc-Prolonging Agents	**Azithromycin** Chloroquine **Chlorpromazine** **Ciprofloxacin** **Clarithromycin**	Clozapine Dolasetron **Droperidol** **Erythromycin** **Flecainide**	Gemifloxacin Goserelin Granisetron **Haloperidol** Leuprolide	**Levofloxacin** **Methadone*** **Moxifloxacin** Ofloxacin	**Ondansetron** Primaquine Propafenone Telavancin
	*Methadone risk with doses ¬> 100mg/day				
Intermediate Risk of QTc Prolonging Agents	Albuterol Alfuzosin Amantadine Amitriptyline Apomorphine Arformoterol Aripiprazole Atazanavir Buserelin Chloral Hydrate Clomipramine Desipramine	Diphenhydramine Doxepin Famotidine **Fluconazole** Formoterol Foscarnet Fosphenytoin Galantamine Hydroxyzine Ibandronate Imipramine Indapamide	Isoflurane Isoproterenol Isradipine Itraconazole Ketoconazole Levalbuterol Lithium Metoclopramide Metronidazole Mirabegron Mirtazapine Moexipril	Nicardipine Norfloxacin Nortriptyline Octreotide Olanzapine Paroxetine Promethazine **Propofol** Ranolazine Risperidone Ritonavir Salmeterol	Sertraline Solifenacin Sulfamethoxazole Tacrolimus Tamoxifen Terbutaline Tizanidine Tolterodine Trazodone Trimethoprim Venlafaxine Voriconazole

* Information obtained from Lexicomp and Crediblemeds.org

RECOMMENDATIONS ON DRUG CHANGE OR MONITORING

	Highest	Moderate	Intermediate
Highest	A	A	A
Moderate	A	A	B
Intermediate	A	B	B

A. Patients who have been on these medications in past should be monitored. Patients who might be starting a medication from this class should be evaluated. If possible, avoid combination. However, if consistent with goals of care, continue with caution. Evaluate the patient's potassium and magnesium levels (if available), adjust dose for renal or hepatic impairment, and monitor patient closely.

B. Continue if both medications are necessary and consistent with goals of care. Evaluate patient's potassium and magnesium levels (if available), adjust dose for renal or hepatic impairment, and monitor patient closely.

References

1. Medical University of South Carolina. (2011, December). MUSC Opioid Analgesic Comparison Chart. Retrieved from MUSC.edu: http://mcintranet.musc.edu/ag-ingq3/calculationswesbite/convchart.pdf
2. Semenchuk, M.R. (2002). Avinza Elan. Current Opinion in Investigational Drugs, 3(9), 1360-1372.
3. Goroll, A., et al. (2009). Primary Care Medicine: Office Evaluation and Management of the Adult Patient. Philadelphia: Lippincott Williams & Wilkins.
4. Reisfield, G. et al. (2007). Rational Use of Sublingual Opioids in Palliative Medicine. Journal of Palliative Medicine, Volume 10(2), 465-475.
5. Robison, J. et al. (1995, December). Sublingual and Oral Morphine Administration. Review and New Findings. The Nursing Clinics of North America, Volume 30(4), 725-743.
6. Stuart-Harris, R. et al. (2000). The Pharmacokinetics of Morphine and Morphine Glucuronide Metabolites after Subcutaneous Bolus Injection and Subcutaneous Infusion of Morphine. British Journal of Clinical Pharmacology, Volume 49(3), 207-214.
7. Global Library of Women's Medicine, Morphine Hydrochloride, Retrieved from Global Library of Women's Medicine: https://www.glowm.com/resources/glowm/cd/pages/drugs/m063.html
8. Jonsson, T. et al. (1988, April). The Bioavailability of Rectally Administered Morphine, Pharmacology & Toxicology, 62(4):203-205.
9. Paddock Laboratories, LLC. (2012, October). Morphine Sulfate Suppository. Retrieved from U.S. National Library of Medicine: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=649d731b-962a-45df-b043-7e0781e8a530&audience=professional
10. Fishman, S. et al. (2010). Bonica's Management of Pain. Baltimore: Lippincott Williams & Wilkins.
11. Davis, M. et al. (2009). Opioids in Cancer Pain. Oxford: Oxford University Press.
12. Kumar, M. G. et al. (2007). Hydromorphone in the Management of Cancer-related Pain: An Update on Routes of Administration and Dosage Forms, Journal of Pharmacy and Pharmaceutical Sciences, Volume 10(4), 504-518.
13. Global Library of Women's Medicine, Hydromorphone hydrochloride, Retrieved from Global Library of Women's Medicine: https://www.glowm.com/resources/glowm/cd/pages/drugs/h012.html
14. Moulin, D. et al. (1991, February 1991). Comparison of Continuous Subcutaneous and Intravenous Hydromorphone Infusions for Management of Cancer Pain, Lancet, Volume 337(8739), 465-468.
15. Ghaly, T. University of Pittsburgh Pain Medicine Program, Retrieved from University of Pittsburgh School of Medicine: http://www.pain.pitt.edu/paincontent/news/Pain%20Symposium%20Poster%20-%20TBG.pdf
16. McPherson, M. L. (2009). Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing (68). Bethesda: ASHP.
17. Chrvala, C. et al. (2011). Abstral (Fentanyl Sublingual Tablets for Breakthrough Cancer Pain), Pharmacy and Therapeutics, Volume 36(2), 2-28.
18. Insys Therapeutics, Inc. (2014, June), Subsys - Sublingual Fentanyl Spray. Retrieved from Insys Therapeutics, Inc.: http://www.insysrx.com/wp-content/uploads/2014/06/INSYS062014.pdf
19. Alberta Health Services. (2005). Long Term Care Formulary: Fentanyl Citrate Injection. Retrieved from Alberta Health Services: http://www.albertahealthservices.ca/hp/if-hp-ltc-pharm-fentanyl.pdf
20. Capper, S. J., & al, e. (2010). Pharmacokinetics of Fentanyl after Subcutaneous Administration in Volunteers. European Journal of Anaesthesiology, Volume 27(3), 241-246.
21. Medical University of South Carolina. (2011, December). MUSC Opioid Analgesic Comparison Chart. Retrieved from MUSC.edu: http://mcintranet.musc.edu/ag-ingq3/calculationswesbite/convchart.pdf
22. Blenheim Pharmacal, Inc. (2010, January). Oxycodone hydrochloride tablet, film coated, extended release. Retrieved from NIH U.S. National Library of Medicine: https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=15783
23. Al-Ghananeem, A. M., et al. (2006). Effect of pH on Sublingual Absorption of Oxycodone Hydrochloride. American Association of Pharmaceutical Scientists: PharmSciTech, Volume 7(1), E163-E167.
24. Kokki, H., et al. (2006). Comparison of Oxycodone Pharmacokinetics after Buccal and Sublingual Administration in Children, Clinical Pharmacokinetics, Volume 45(7), 745-754.
25. Bruera, E. H. (2014). Textbook of Palliative Medicine and Supportive Care. Boca Raton: CRC Press.
26. Leow, K., et al. (1992). Comparative Oxycodone Pharmacokinetics in Humans after Intravenous, Oral, and Rectal Administration, Therapeutic Drug Monitoring, 14(6):479-484.
27. Lintz, W. et al. (1998), Pharmacokinetics of Tramadol and Bioavailability of Enteral Tramadol Formulations. 3rd Communication: suppositories, Arzneimittel-Forschung, 48(9):889-899.
28. Gadani, H., et al. (2010), Comparative Study of the Analgesic Efficacy of Rectal Tramadol versus Intravenous Tramadol for Adult Tonsillectomy, Anesthesia Essays and Researches, 4(2):102-105.
29. Sloan, P. (2008). Review of Oral Oxymorphone in the Management of Pain, Journal of Therapeutics and Clinical Risk Management, Volume 4(4), 777-787.
30. Endo Pharmaceuticals Inc. (2007, January), Opana ER (Oxymorphone Hydrochloride Extended Release), Retrieved from NIH U.S. National Library of Medicine: https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=3354
31. Shorr, R. (2007), Drugs for the Geriatric Patient, Philadelphia: Saunders Elsevier.
32. University of Maryland Baltimore Washington Medical Center, Oxymorphone. Retrieved from University of Maryland Baltimore Washington Medical Center: http://www.mybwmc.org/library/41/095800
33. Dale, O., et al. (2004). Bioavailabilities of Rectal and Oral Methadone in Healthy Subjects, British Journal of Clinical Pharmacology, 58(2):156-162.
34. International Association for Hospice and Palliative Care, (2013, January), WHO Essential Medicines in Palliative Care. Retrieved from World Health Organization: http://www.who.int/selection_medicines/committees/expert/19/applications/PalliativeCare_8_A_R.pdf
35. Caille, G. et al. (1983), Pharmacokinetics of Two Lorazepam Formulations, Oral and Sublingual, After Multiple Doses, Biopharmaceutics & Drug Disposition, Volume 4(1), 31-42.
36. Black, F., et al (2008). INCTR Palliative Care Handbook. Brussels: INCTR.
37. Global Library of Women's Medicine, Lorazepam. Retrieved from Global Library of Women's Medicine: https://www.glowm.com/resources/glowm/cd/pages/drugs/kl037.html
38. Shorvon, S. et al. (2009). The Treatment of Epilepsy. Oxford: Blackwell Publishing.
39. Clemens, P. (2006). Alternate Routes of Antiepileptic Drug Administration: A Clinical Study of Rectally Administered Oxcarbazepine Suspension. Ann Arbor: University of Minnesota.
40. Graves, N. et al. (1987), Bioavailability of Rectally Administered Lorazepam, Clinical Neuropharmacology, 10(6):555-559.
41. Sheehan, D. et al. (2007), The Speed of Onset of Action of Alprazolam-XR Compared to Alprazolam-CT in Panic Disorder, Psychopharmacology Bulletin, Volume 40(2), 63-81.
42. Nursing Times (2004), Drugs Clinical: Diazepam. Nursing Times, Vol 100(45), 31.
43. Manor, D. et al. (1989). Muscle Fibre Necrosis Induced by Intramuscular Injection of Drugs, British Journal of Experimental Pathology, Vol 70(4), 457-462.
44. Johnstone, L. et al. (2011, December), Guidelines for the Use of Subcutaneous Medications in Palliative Care.
45. Brusco, L. (2002), Choice of Sedation for Critically Ill Patients: A Rational Approach, Advanced Studies in Medicine, Vol 2(9), 343-349.

References *Continued*

46. Harris, D. et al. (2009), Management of Terminal Hemorrhage in Patients with Advanced Cancer: A Systematic Literature Review, Journal of Pain and Symptom Management, Vol 38(6), 913-927.

47. Kraus, G. et al. (1989), Pharmacokinetic Studies Following Intravenous and Rectal Administration of Midazolam in Children, Der Anaesthesist, 38(12):658-663.

48. Payne, K. et al. (1989), The Pharmacokinetics of Midazolam in Pediatric Patients, European Journal of Clinical Pharmacology, 37(3):267-272.

49. Holm-Knudsen, R. et al. (1990), Rectal Administration of Midazolam versus Diazepam for Pre-anesthetic Sedation in Children, Anesthesia Progress, 37 (1):29-31.

50. Drug Facts & Comparisons online database, accessed online Dec. 2015.

51. Drugs.com, accessed online Dec. 2015 at: http://www.drugs.com

52. Physician's Desk Reference (PDR), accessed online Dec. 2015 at: http://www.pdr.net

53. Lexicomp online database, Lexi-Comp Inc., accessed online Nov. 2019

54. Lazanda manufacturer website for healthcare professionals, accessed online Dec. 2015 at: http://www.lazanda.com/hcp

55. Medscape, accessed online Nov. 2019 at: http://www.medscape.com

56. Micromedex online database, accessed online Nov. 2019 at: http://micromedex.com/

57. UpToDate online database, accessed online Dec. 2015 at: http://www.uptodate.com/home

58. Khanna IS, Pillarisetti S. Buprenorphine – an attractive opioid with underutilized potential in treatment of chronic pain. J Pain Res. 2015; 8: 859–870.

59. Trescot AM, Datta S, Lee M, Hansen H. Opioid Pharmacology. Pain Physician. 2008 Mar;11(2 Suppl):S133-53.

60. Umbricht A, Huestis MA, Cone EJ, Preston KL. Effects of high-dose intravenous buprenorphine in experienced opioid abusers. J Clin Psychopharmacol. 2004 Oct;24(5):479-87.

61. Extended-release hydrocodone (Hysingla ER) for pain. Med Lett Drugs Ther. 2015 May 11;57(1468):71-2.

62. Bekhit MH. Profile of extended-release oxycodone/acetaminophen for acute pain. J Pain Res. 2015; 8: 719–728.

63. Bain, KT. Management of Chronic Insomnia in Elderly Persons. Am J Geriatr Pharmacother. 2006;4(2):168-192.

64. Belbuca manufacturer website for healthcare professionals, accessed online Nov. 2019 at http://www.belbuca.com/hcp