

Painweek.

ADVANCED EDUCATION

CERTIFICATION SERIES



PALLIATIVE CARE

Genitourinary Symptoms

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Disclosures



Learning Objectives

At the conclusion of this presentation the participant will be able to:

List 5 potential etiologies of bladder spasms in the palliative care patient population

Identify common adverse effects associated with anticholinergic and beta-3-agonist medications used to treat overactive bladder

Describe strategies for the prevention and management of urinary tract infections in advanced illness

Bladder Spasms

- Affects 7%-27% of men and 9%-43% of women
- Many potential etiologies
- Can have both nociceptive and neuropathic components
- Often difficult to treat



Gormley. *J Urol*. 2014;188:2455-2463.

Etiology of Bladder Spasms

Urinary tract infection

Indwelling catheter

Genitourinary malignancy

Ingestion of chemical irritants (eg, diet soda, caffeine)

Constipation

Obstruction of bladder outflow (eg, nonemptying catheter due to blood clots)

Disinhibition from interruption of upper motor neurons

Medications

Clinical Evaluation of Bladder Spasms

- Determine if the bladder is emptying properly
 - If inpatient, consider ultrasound to assess postvoid residual (PVR)
 - If home or hospice setting, examine suprapubic area for bladder fullness
 - If not emptying properly, consider urethral catheterization
- Evaluate for reversible causes
 - Medications
 - Constipation
- Rule out urinary tract infection (if suspected) with urinalysis

Management of Bladder Spasms

Pharmacologic Treatment

- Bladder muscle relaxants
- Bladder emptying agents
- Medications that calm surface irritation

Interventional Procedures

- Onabotulinum toxin
- Surgical resection of bladder tumor
- Lithotripsy of stones
- Pelvic physical therapy
- Other

De. Fast Facts & Concepts #337. Palliation of bladder spasms. Palliat Care Network Wisconsin.

Pharmacologic Treatment of Bladder Spasms

- **Bladder muscle relaxants**

- Anticholinergics

- Oxybutynin IR 5-15 mg po TID; ER qday
- Tolterodine IR 2-4 mg po BID
- Solifenacin 5-10 mg po daily
- Dicyclomine 20 mg up to 4x/day
- Adverse effects:
 - Xerostomia, constipation

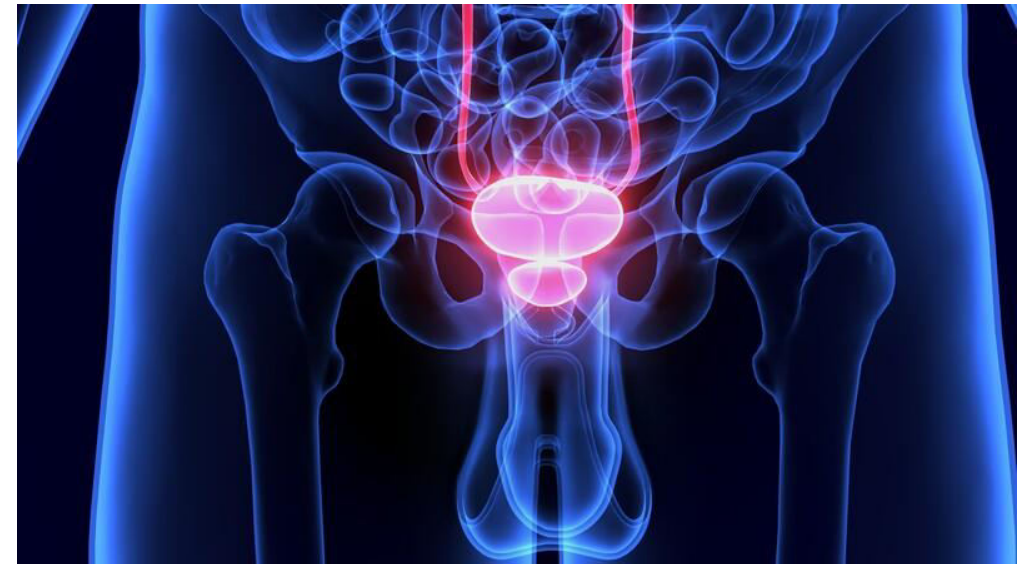
- Beta-3 agonists

- Mirabegron 25-50 mg po daily
- Adverse effects:
 - Hypertension
 - Xerostomia
 - Urinary tract infections
 - Potentiation of metoprolol

- **Bladder emptying agents**

- Alpha blockers

- Tamsulosin 0.5 mg po daily
- Terazosin 2-10 mg po daily
- Adverse effects:
 - Orthostatic hypotension



De. Fast Facts & Concepts #337. Palliation of bladder spasms. Palliat Care Network Wisconsin.

Anticholinergic Side Effects



Urinary retention



Dry mouth, constipation



Feeling hot, decreased sweating



Tachycardia



Blurred vision, dry eyes



Sedation, dizziness, confusion, hallucinations

De. Fast Facts & Concepts #337. Palliation of bladder spasms. Palliat Care Network Wisconsin.

Pharmacologic Treatment of Bladder Spasms



- **Medications that calm surface irritation**
 - Phenazopyridine 100-200 mg po TID PRN
 - Adverse effects:
 - May stain clothing
 - Methemoglobinemia
 - Belladonna and opium suppository
 - Adverse effects: opioid side effect profile
 - Diazepam 5-10 mg PR or intravaginally q8h PRN
 - NSAIDs
 - Corticosteroids

De. Fast Facts & Concepts #337. Palliation of bladder spasms. Palliat Care Network Wisconsin.

Interventional Procedures for Bladder Spasms

- Onabotulinum toxin injection to detrusor muscle
 - Urinary retention is a known side effect
 - May improve spasms with indwelling catheter
- Surgical resection of bladder tumors
- Lithotripsy of stones
- Pelvic physical therapy
- Intravesical baclofen, bupivacaine, \pm morphine
- Nerve blockade
- Pessary



De. Fast Facts & Concepts #337. Palliation of bladder spasms. Palliat Care Network Wisconsin. Oransanu. *Indian J Urol*. 2013;29(1):2-11. *Pract Pain Manag*. 2011;5(3). *J Palliat Care*. 2018;29(1):49-51. Gulati. *Pain Physician*. 2011;14(3):305-310.

Self-Assessment!

All of the following are common adverse effects associated with anticholinergic medications except:

- A. Blurred vision
- B. Excess secretions
- C. Constipation
- D. Urinary retention
- E. Sedation



Self-Assessment!

All of the following are common adverse effects associated with anticholinergic medications except:

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- D. Urinary retention
- E. Sedation



Overactive Bladder (OAB)

- The combined presence of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of UTI or other obvious pathology
- Affects an estimated 33 million Americans
 - Women are more likely to suffer from OAB than men
 - Incidence increases with age
- Many potential etiologies
- Best evidence for nondrug interventions + drug therapy



Leron. *Curr Urol.* 2018;11(3):117-125.

Etiology of Overactive Bladder

Urological

- Urinary tract infection
- Detrusor overactivity
- Bladder calculus
- Urethral obstruction

Gynecological

- Pregnancy
- Stress incontinence
- Pelvic mass
- Previous pelvic surgery
- Radiation cystitis/fibrosis
- Postmenopausal urogenital atrophy
- Sexually transmitted infection

Medical

- Medications
- Upper motor neuron lesion
- Impaired kidney function
- Heart failure
- Diabetes
- Anxiety

Medication-Related Causes

Alpha-adrenergic agonists

(eg, phenylephrine, pseudoephedrine)

Alpha-adrenergic antagonists

(eg, prazosin, terazosin, doxazosin)

Anticholinergic drugs

(eg, diphenhydramine, nortriptyline, amitriptyline)

Antipsychotics

(eg, chlorpromazine, haloperidol)

Acetylcholinesterase inhibitors

(eg, donepezil, galantamine, rivastigmine)

Antineoplastic drugs

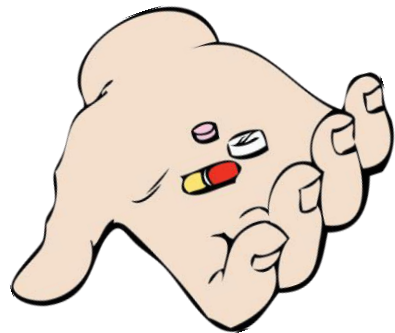
(eg, vincristine)

Calcium channel blockers

(eg, amlodipine, nifedipine, diltiazem, verapamil)

Diuretics

(eg, furosemide, bumetanide)



Opioids

(eg, morphine, oxycodone, hydromorphone, methadone, fentanyl)

Benzodiazepines

(eg, alprazolam, diazepam)

Panesar. *Urology*. 2014;39(8):24-29.

Nonpharmacologic Treatment of OAB



- Fluid restriction (1.5-2 L/day)
- Bladder training/timed voiding
- Limiting bladder irritating foods/drinks
 - Caffeine (eg, coffee, tea, soda)
 - Alcohol
- Weight loss
- Physical/pelvic therapy
- Biofeedback
- Intravaginal devices
- Pessaries

Pharmacologic Treatment of OAB

- **Beta-3 agonists**

- *Medications:*

- **Mirabegron** 25-50 mg PO daily
 - **Vibegron** 75 mg PO daily
 - Can be crushed

- *Mechanism:* stimulates the receptors in the bladder responsible for smooth muscle relaxation

- *Adverse effects:*

- Hypertension (mirabegron only; not seen in trials of vibegron)
 - Headache
 - GI effects (nausea, constipation)
 - Rhinorrhea/nasopharyngitis

- Similar efficacy and fewer adverse effects than anticholinergic medications

online-lexi-com.ezproxymcp.flo.org/lco/action/doc/retrieve/docid/patch_f/3819763.

online-lexi-com.ezproxymcp.flo.org/lco/action/doc/retrieve/docid/patch_f/7050270.

Pharmacologic Treatment of OAB

- **Anticholinergic drugs**

- *Medications:*

- **Darifenacin** 7.5-15 mg PO once daily
- **Fesoterodine** 4-8 mg PO once daily
- **Oxybutynin** IR 5 mg PO 2-4x/day;
ER 5-30 mg PO once daily; TD patch: 3.9 mg BIW
- **Solifenacin** 5-10 mg PO once daily
- **Tolterodine** IR 1-2 mg PO BID;
ER 2-4 mg PO once daily
- **Trospium** IR 20 mg PO once daily to BID;
ER: 60 mg PO once daily

- *Mechanism:* Block muscarinic receptor stimulation by acetylcholine, reducing smooth muscle contraction of the bladder
- Typically, less expensive than beta-3 agonists; older medications

- *Adverse effects:*



Urinary retention



Dry mouth, constipation



Feeling hot, decreased sweating



Tachycardia



Blurred vision, dry eyes



Sedation, dizziness, confusion, hallucinations

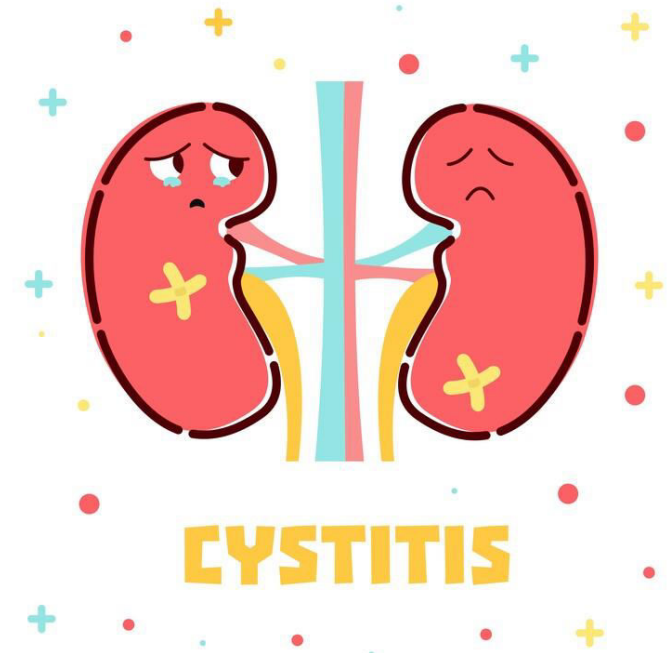
Deprescribing Tips and Tricks

- OAB medications decrease incontinence episodes and/or frequency by ~1 episode/day
- If a patient has a catheter, discontinue their OAB medication(s).
 - Exception: Significant bladder spasms or discomfort from catheter
- Many patients stop taking OAB medications due to intolerable side effects
- Regularly review patients' medications and consider overall anticholinergic and pill burden

Yamada. *Pharmacol Ther.* 2018;189:130-148.

Urinary Tract Infections (UTIs)

- Clinical diagnosis, laboratory confirmation
- Most common pathogens include *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis*, and *Staphylococcus saprophyticus*
- Culture and sensitivity typically only needed if symptoms persist after completion of treatment
- Diagnostic imaging not usually indicated
- Do not treat asymptomatic bacteriuria
 - Rising rates of antimicrobial resistance



Vagios. *Microb Pathog*. 2020;148:104544.

Sihra. *Nat Rev Urol*. 2018;15(12):750-776.

Treatment of UTIs

Acute, uncomplicated

- Nitrofurantoin 100 mg po BID x 5 days
- Trimethoprim/sulfamethoxazole 160mg/800 mg (1 DS tab) PO BID x 3 days
- Fosfomycin 3 g PO x 1 dose

Complicated

- **Mild-to-moderately ill**
 - Levofloxacin 500 mg IV/PO q24h
 - Ciprofloxacin 500 mg PO BID or 400 mg IV q8-12h
- **Severely ill, recent fluoroquinolone use, or long-term care facility resident**
 - Cefepime 2 g IV q12h
 - Ceftazidime 2 g IV q8h
 - Ceftazidime/avibactam 2000mg/500mg IV q8h
 - Ceftolozane/tazobactam 1500 mg IV q8h
 - Imipenem 500 mg IV q6h
 - Meropenem 1 g IV q8h
 - Doripenem 500 mg IV q8h

*Johns Hopkins ABX Guide, Johns Hopkins University, 2021.
Hooton. Clin Infect Dis. 2011;52(5):e103-120.*

EAU Guidelines. Edn. presented at the EAU Annual Congress Milan Italy 2021. ISBN 978-94-92671-13-4.

Recurrent UTI (rUTI)

- Definition
 - ≥ 2 episodes within a 6-month period
 - ≥ 3 episodes within a 12-month period
- Risk Factors
 - Premenopausal women: Frequent sexual intercourse, use of spermicide, short distance between urethra and anus
 - Postmenopausal women: Incontinence, cystocele, high postvoid residual, premenopausal UTIs, vaginal and periurethral atrophy due to decreased estrogen
- Prevention/treatment
 - Antibiotics
 - Nitrofurantoin
 - Trimethoprim/sulfamethoxazole
 - D-mannose
 - Lactobacillus
 - Cranberry
 - Topical vaginal estrogen

Antibiotics

- Nitrofurantoin 50-100 mg PO qhs
- Trimethoprim/sulfamethoxazole 40mg/200mg (1/2 SS tab) PO qhs or TIW
- Trimethoprim 100 mg PO qhs
- Ciprofloxacin 125 mg PO qhs
- Norfloxacin 200 mg PO qhs
- Cephalexin 125-250 mg PO qhs

Johns Hopkins ABX Guide, The Johns Hopkins University, 2021.

Hooton. *Clin Infect Dis*. 2011;52(5):e103-120.

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Antibiotics at End of Life



- Antibiotics tend to be overused in the final weeks of life
- Can be particularly helpful for UTI, 60%-92% symptomatic improvement noted in systematic reviews
- Onset of symptom benefit: 24-48h
- Oral options preferred

Rosenberg. *J Palliat Med.* 2013;16(12):1568-1574.

Reinbolt. *J Pain Symptom Manage.* 2005;30(2):175-182.

White. *J Pain Symptom Manage.* 2003;25(5):438-443.

D-Mannose

- What is it?
 - Naturally occurring carbohydrate, found in fruits and vegetables
- How does it work?
 - Binds to bacteria in the bladder, preventing adherence
- How is it given?
 - *Prevention* – 2 g PO once daily or 1 g PO BID
 - *Treatment* – 1.5 g PO BID x 3 days, then once daily x 10 days; or 1 g PO TID x 14 days
- Clinical evidence?
 - Reduction in the incidence of recurrent UTIs and increased duration between episodes of recurrences
 - Significant reduction in dysuria, frequency, urgency, tenesmus, suprapubic pain, and nocturia

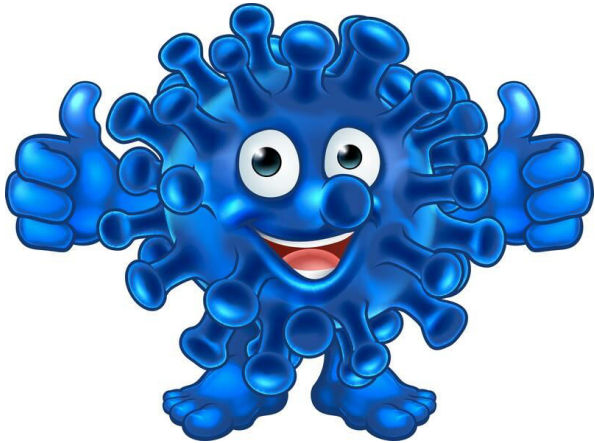


NCBI: Eur Urol Focus. 2020 Sep 21:S2405-4569(20)30263-7.

[Am J Obstet Gynecol 2020; 223:265.e1–265.e13.](#)

Barea. *Curr Opin Urol.* 2020;30(6):845-852.

Lactobacillus



- Most common genus in vaginal microbiota
- Inverse relationship between lactobacillus and E. coli
- Heterogeneity of available studies
 - Different lactobacillus species, formulations, dosages
- Conflicting data
 - Cochrane review found no significant reduction in rUTI
 - RCT of combination probiotics + cranberry extract vs placebo found a significant reduction in rUTIs

Vagios. *Microb Pathog*. 2020;148:104544.

[Am J Obstet Gynecol 2020; 223:265.e1–265.e13.](#)

Barea. *Curr Opin Urol*. 2020;30(6):845-852.

Schwenger. *Cochrane Database Syst Rev*. 2015;CD008772.

Koradia. *Expert Rev Anti Infect Ther*. 2019; 17:733-740.

Cranberry

- Efficacy thought to be due to presence of proanthocyanidins
 - Inhibitory effect on motility of *Pseudomonas aeruginosa*, *Escherichia coli* and *Proteus mirabilis*
 - Antiadherence effect
- Conflicting evidence
 - *Cochrane review*: cranberry products didn't reduce occurrence of symptomatic UTI over 12 months in women with rUTI (RR 0.74, 95% CI 0.42-1.31)
 - *Maki et al* studied 240 ml cranberry beverage/day vs placebo; found reduction in clinical rate of UTI and pyuria
- Likely low risk



Jepson. *Cochrane Database Syst Rev.* 2012;10:CD001321.

J Am Coll Nutr. 2018; 37:121–126.

Phenazopyridine

- Used for symptomatic relief only (not treatment)
- *Mechanism:* Exerts local anesthetic or analgesic action on urinary tract mucosa
- *Dose:* 200 mg PO TID after meals for up to 2 days
 - Can we continue for longer at end of life??
 - Safety analysis of long-term phenazopyridine use (>14 days) for radiation cystitis showed no difference in adverse effects
- *Patient counseling:*
 - May turn urine and sclera red or orange
 - May stain contact lenses, fabric, or clothing

Shore. *J Onc Pharm Pract.* 2019;26(2):306-311.

Phenazopyridine. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated and accessed 12/2021].

Self-Assessment!

WHAT HAVE YOU LEARNED?











AD is a 72 year old female who was admitted to hospice with a diagnosis of metastatic breast cancer and an estimated prognosis of 2-3 months. She is reporting uncomfortable symptoms consistent with UTI. What is the most appropriate management strategy?

- A. Begin preventative therapy with D-mannose
- B. Begin lactobacillus
- C. Treat her symptomatically with phenazopyridine
- D. Begin an oral antibiotic that will most likely target the causative organism

Self-Assessment!

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WHAT HAVE YOU LEARNED?











Conclusion

- Bladder spasms may be very uncomfortable and difficult to treat
- Pharmacologic treatment of bladder spasms includes bladder muscle relaxants, bladder emptying agents, and medications that calm surface irritation of the bladder
- Overactive bladder is a common occurrence and may be due to a urological, gynecological, or medical cause
- Overactive bladder may be treated with a beta-3 agonist or anticholinergic medication
- Urinary tract infections are likely to cause discomfort and generally warrant treatment
- Prophylactic treatment may be offered to prevent a repeated UTI
- Phenazopyridine may relieve discomfort associated with cystitis

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