PHARMACOLOGY IN UROLOGY

Jennifer Gonzalez, MSN, APRN

OBJECTIVES

- Provide a brief overview of urologic conditions commonly seen in primary care settings
- Understand the pharmacologic action of commonly prescribed medications for urologic conditions
- Understand the side effects for commonly prescribed urologic medications
- Understand the contraindications for commonly prescribed urologic medications
- Understand the cost considerations for commonly prescribed urologic medications

INCONTINENCE

- There are two types of incontinence: Stress and Urge incontinence
- Stress incontinence occurs when the individual coughs, laughs, sneezes or with any activity
- Overactive bladder is a clinical diagnosis defined by the International Continence Society as the presence of “urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary infection or other obvious pathology (ICS, 2021)
- Isolated nocturia is rarely a urologic issue, but rather a symptom of another condition

INCONTINENCE MEDICATIONS

- Antimuscarinics
  - Oxybutynin
  - Tolterodine
  - Darifenacin
  - Solifenacin
  - Trospium
  - Fesoterodine
  - Propiverine
- Beta3-adrenergic medication
  - Mirabegron
  - Vibegron

ANTIMUSCARINICS PHARMOCOKINETICS

- Action: target muscarinic receptors in the body. There are a total of 5 types of muscarinic receptors in the bladder, where M3 muscarinic receptors mediate the contraction of the bladder smooth muscles.
- M1 receptors are important in cognitive function and memory. Blockade of central M1 has been implicated in cognitive impairment, such as memory loss.
- M2 receptors are involved in the regulation of heart rate and heart rate variability
- Because these medications are nonselective, concerns have been raised over the impact these medications can have on cognitive function as well as cardiovascular risk

ANTIMUSCARINICS DOSING

- Oxybutynin
  - IR 2.5 mg -5 mg TID, max 20 mg / day
  - ER: 5-30 mg/day, max 30 mg per day
  - Transdermal 3.9 mg patch twice weekly
  - Topical gel: 100 mg/day
- Tolterodine
  - IR 1-2 mg BID
  - ER: 4 mg/day
- Darifenacin
  - 7.5-15 mg , max 15 mg/day

ANTIMUSCARINIC DOSING, CONTINUED

- Trospium
  - IR 20 mg bid
  - ER: 60 mg daily
- Solifenacin
  - 5-10 mg, max 10 mg per day
- Fesoterodine
  - 4-8 mg, max 8 mg per day
- Propiverine
  - IR: 15 mg daily up to TID
  - ER: 30 mg per day

ANTIMUSCARINICS METABOLISM

- Oxybutynin
  - Metabolized by the liver, but no adjustment necessary for liver dysfunction
- Tolterodine
  - Metabolized by the liver
  - Renal and liver impairment dosage 2 mg/day
- Trospium
  - Ester hydrolysis
  - Renal dosing; 20 mg/day at HS
  - No liver dosing
- Darifenacin
  - Metabolized by the liver
  - No renal dosing
  - Moderate hepatic dysfunction: max dose 7.5 mg/day

METABOLISM

- Solifenacin
  - Hepatic
  - Severe renal dysfunction max; 5 mg/day
  - Moderate hepatic dysfunction max: 5 mg/day
  - Severe hepatic dysfunction: do not use
- Fesoterodine
  - Hepatic
  - Severe renal impairment:: max 4 mg per day
  - Severe hepatic dysfunction: do not use
- Propiverine
  - Hepatic
  - Renal dosing: unknown if needed
  - Severe hepatic dysfunction: dosing adjustment may be necessary

ANTIMUSCARINICS

- Side effects: dry mouth, constipation, urinary retention, fatigue, confusion, unsteady gait, mouth sores, dry eyes
- All are on the Beer's list specifically in elderly patients with constipation and those with deliurum, dementia or cognitive impairment
- Contraindications: narrow angle glaucoma or can be used with great caution with approval from treating ophthalmologist, urinary retention, delayed gastric emptying, gastroparesis
- Onset of action is typically about 2 weeks, but efficacy can take as long as 12 weeks

B3-ADRENOCEPTOR AGONISTS

- Myrbetriq (mirabegron)~beta-3 adrenergic agonist which increases bladder capacity. The drug contains an anticholinergic agent, which is a substance that blocks the neurotransmitter acetylcholine in the central and the peripheral nervous system and stops involuntary bladder contractions. The drug also relaxes the detrusor urinae muscle during the storage phase
  - Dosing: 25-50 mg daily
  - Can be combined with solifenacin 5-10 mg daily. This is the only anti-muscarinic that has been FDA approved to use in combination with mirabegron
  - Side effects: hair loss, increase in blood pressure, urinary retention
  - Contraindicated: uncontrolled hypertention, angioedema, urinary retention
  - Metabolized in the liver, should prescribe cautiously with concurrent use of other drugs metabolized in the CYP450 and CYP2D6 system. Common medications include: amiodarone, cimetidine, diphenhydramine, fluoxetine, paroxetine, quinidine, ritonavir, terbinafine, amitriptyline, carvedilol, codeine, donepezil, haloperidol, metoprolol, paroxetine, risperidone, and tramadol
  - Efficacy is 6-8 weeks
  - It is thought that neuro-cognitive issues are not as much of a concern with mirabegron, but needs to be further investigated

B3-ADRENOCEPTOR AGONISTS

- Gemtesa (virbegron): just released in April 2021
  - Selective human beta-3 adrenergic receptor agonist. Activation of beta-3 adrenergic receptor increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling
  - Metabolism: Metabolism plays a minor role in elimination of vibegron. Predominately metabolized by CYP3A4
  - Dosing: 75 mg daily
  - Side effects: headache, constipation, urinary retention, dry mouth, uti
  - Not recommended in ESRD or severe liver dysfunction
  - No significant increase in blood pressure
  - Will increase digoxin levels, use cautiously in combination with digoxin
  - Efficacy up to 12 weeks

NOCTURNAL ENURESIS PHARMOCOKINETICS

- DDAVP ~ suppresses urinary production at night and decreases intravesicular pressure
  - Comes in tablets and nasal sprays
  - Dosing 0.2 mcgs to 0.6 mcgs at bedtime
  - Restrict fluids 2 hours prior to bedtime
  - Side effects: Mild: nasal irritation, nosebleeds, and headache Severe: emotional disturbances, aggressive behaviors and nightmares, hyponatremia
  - Use with caution in renal impairment

- TCA ~ most commonly used is imipramine; action is not well understood in nocturnal enuresis
  - It is thought that the anticholinergic effect of the drug may result in a decrease in bladder contractility that leads to increased bladder filling and improved functional bladder capacity
  - Dosing: 25-75 mg at bedtime
  - Side effects: dry mouth, constipation, fatigue, weight gain, headache, dizziness, blurred vision
  - Metabolized by the liver

BPH

- A benign enlargement of the prostate
- Symptoms include frequency, urgency, dribbling, incomplete emptying, nocturia, hesitancy, intermittency
  - Alpha blockers
    - Tamsulosin
    - Alfuzosin
    - Silodosin
    - Terazosin
    - Doxazosin
  - 5 Alpha-Reductase Inhibitors
    - Finasteride
    - Dutasteride

BPH MEDICATIONS

- Alpha Blockers ~ Smooth-muscle tension is mediated by alpha-1-adrenergic receptors; therefore, alpha-adrenergic receptor–blocking agents should theoretically decrease resistance along the bladder neck, prostate, and urethra by relaxing the smooth muscle, thus allowing easier passage of urine
  - Tamsulosin, alfuzosin, silodosin have less blood pressure affect than doxazosin and terazosin
  - Side effects: retrograde ejaculation, postural hypotension, rhinitis, weakness, fatigue
  - Metabolized by the liver
  - Early onset of efficacy, less than one week
  - Dosing
    - Tamsulosin 0.4-0.8 mg per day
    - Alfuzosin: 10 mg with food
    - Silodosin: 4-8 mg per day
    - Terazosin: 5 mg per day, titrate up from 1 mg per day
    - Doxazosin: 8 mg per day, titrate up from 2 mg per day

BPH MEDICATIONS

- 5 Alpha-Reductase Inhibitors~block the conversion of testosterone to dihydrotestosterone (DHT). DHT has a more potent effect on the prostate and suppression with 5-ARIs leads to a reduction in prostate volume/PSA and decrease in symptoms associated with bladder outlet obstruction
  - Side effects: ED, gynecomastia, ejaculatory disorders, low libido, breast tenderness and rash
  - Metabolized: liver
  - Long time to efficacy: 3-6 months
  - No difference between finasteride and dutasteride efficacy
  - PSA correction: because 5 alpha reductase inhibitors reduce prostate volume, you must double the psa when screening
  - Dosing
    - Finasteride 5 mg daily
    - Dutasteride 0.5 mg daily

ERECTILE DYSFUNCTION

- Inability of a man to maintain an erection sufficient for satisfying sexual activity
- PDE-5i~Phosphodiesterase type 5 (PDE5) is the predominant phosphodiesterase enzyme in the penis. PDE5 hydrolyzes cyclic guanosine monophosphate (cGMP) to the inactive form 1-prime guanosine monophosphate (GMP). cGMP is a key regulator of calcium hemostasis and smooth muscle contraction in the penile vasculature; hence, depletion of cGMP by action of PDE5 will tend to oppose penile erection. PDE5i are competitive inhibitors of PDE5 by binding to the catalytic domain and hence promote high levels of cGMP in the penile vasculature
  - Sildenafil
  - Tadalafil
  - Vardenafil
  - Avanafil
  - Lodenafil
  - Mirodenafil
  - Udenafil

ERECTILE DYSFUNCTION MEDICATIONS

- Most commonly used are sildenafil, tadalafil, and vardenafil
  - Side effects: flushing, headache, nasal congestion, myalgia, visual changes
  - Contraindications: active use of nitroglycerin
  - Renal and Liver considerations: start at lowest possible dose
  - Onset of efficacy: 30 minutes to 2 hours
  - Duration: tadalafil lasts the longest, allowing for response up to 48 hours after dosing
  - Dosing
    - Sildenafil 25-100 mg prn Must take an hour before, on an empty stomach, with no alcohol
    - Tadalafil 5-20 mg prn
    - Vardenafil 5-20 mg prn
- Tadalafil 5 mg can be given daily and it can decrease symptoms of enlarged prostate as well as provide erectile dysfunction support
- Oral medications rarely cause priapism

ERECTILE DYSFUNCTION

- Urethral suppositories: Muse: prostaglandin, not used often, will use in conjunction with penile prosthesis
- Intracorporal injections: bimix, trimix, quadmix
  - Injection into the cavernosa
  - Erection within 15 minutes
  - Most common cause of medication induced priapism
- Use both cautiously in individuals with sickle cell anemia or trait, thrombocytopenia, polycythemia and multiple myleloma as they are already at an increased risk of priapism
- Adverse events: penile pain and plaque formation

HYPOGONADISM

- Low serum testosterone in the presence of symptoms consistent with the disorder, without regard to spermatogenic potential
- Symptoms: low libido, low energy, low motivation, sleep disturbances, decreased muscle mass/strength, breast enlargement/tenderness, poor concentration, hot flashes and sweating
- Diagnosis: an early morning testosterone (prior to 10 am), if less than 300 ng/dL a repeat level should be drawn with a hematocrit, LH, prolactin, estradiol (based on other symptoms), and psa
  - Testosterone Cypionate IM
  - Testim, Androgel, compounded testosterone gel
  - Natesto (nasal spray)
  - Axiron (axillary)
  - Testopel (subcutaneous pellets)

HYPOGONADISM

- Positive effects of testosterone therapy
  - Increased lean body mass
  - Decreased fat mass
  - Increased bone density
  - Increased libido
  - Improved erections
  - Improved response to PDE5i
  - Improved fasting glucose
  - Improved Hgb A1C
  - Improved triglycerides and total cholesterol
  - Improved mood
  - Beneficial effects on cardiac perfusion, ischemic threshold, exercise threshold, cardiac output

MALE HYPOGONADISM

- **Positive Effects of Testosterone Therapy**
  - Increased lean body mass
  - Decreased fat mass
  - Increased bone density
  - Increased libido
  - Improved erections
  - Improved response to PDE5i
  - Improved fasting glucose
  - Improved Hgb A1C
  - Improved triglycerides and total cholesterol
  - Improved mood
  - Beneficial effects on cardiac perfusion, ischemic threshold, exercise threshold, cardiac output
  - No increased risk of prostate cancer

- **Negative Effects of Testosterone Therapy**
  - Increased sebum
  - Increased hair loss
  - Increased acne
  - Increased hemoglobin
  - Increased DVT
  - Exogenous T used alone results in decreased spermatogenesis
  - Hypothetical increased risk of gynecomastia and breast cancer
  - Conflicting results on rising psa
  - Early worsening of OSA with severe baseline symptoms
  - Unclear affect on localized prostate cancer or treated prostate cancer
  - Worsens advanced or metastatic prostate cancer

HYPOGONADISM MEDICATIONS

- IM injections
  - Cypionate
    - 50 mg to 200 mg weekly/bi-weekly/monthly
  - Aveed
    - 750 mg IM x 1, again at 4 weeks then every 10 weeks
- Topical
  - Androderm
    - 2-6 mg every two weeks (patch)
  - Androgel
    - 2-3 pumps per day
  - Testim
    - 50-100 mg daily
  - Axiron
    - 1-2 clicks daily
  - Fortesta
    - 1-7 pumps daily
- Nasal Spray
  - Natesto
    - 1 pump per nostril bid to tid
- Pellets
  - Testopel
    - 150 -450 mg every 3-6 months

MALE HYPOGONADISM

- Monitoring guidelines
  - Early morning testosterone 4-6 weeks after initiation and any dose changes and every six months while on therapy
  - Hematocrit 4-6 weeks after initiation and any dose changes and every six months while on therapy
    - significant polycythemia (Hct >54%) may require dose adjustment, periodic phlebotomy, or temporary/permanent T discontinuation
  - PSA annually
- Contraindications
  - Metastatic or locally advanced prostate cancer
  - Breast cancer
  - Hematocrit level >54%
  - Untreated OSA
  - Untreated severe congestive heart failure
  - Relative contraindication in those with treated or low-grade untreated prostate cancer

COST CONSIDERATIONS

- Incontinence
  - Most of the anti-muscarinics are fairly expensive. Good RX is a good option for patients and cost.
  - Myrbetriq and Gemtesa are very expensive
- BPH
  - All are generally well covered
  - Silodosin is usually the most difficult to get covered
  - Just heard finasteride is free at Sam's clubs
- Low T
  - IM injections are well covered
  - Topicals are not typically well covered.
    - Compounded pharmacies are helpful here
    - Can use fear of needles to help
  - Pellets are covered after other therapies are failed
    - Can use fear of needles
- ED
  - PDE5i
    - Sildenafil and tadalafil are now available in generic
    - Good RX works well to help cover
  - ICI
    - All compounded, expensive, not covered

QUESTIONS???

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