Medications Used in Urinary Incontinence

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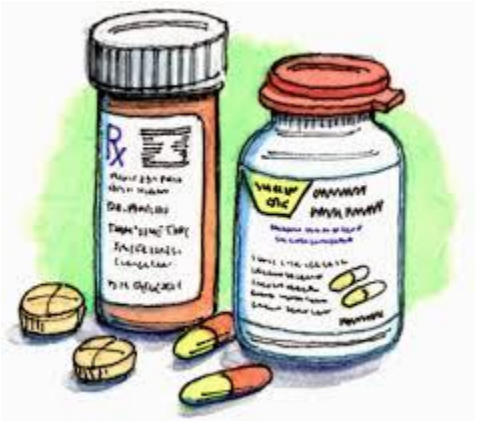
Treatment of Urinary Incontinence (UI)

- 1st line in managing overactive bladder and urgency UI
  - Lifestyle changes
  - Bladder training

- 1st line in managing stress UI
  - Lifestyle changes
  - Pelvic floor muscle exercises

- Then…



PHARMACOLOGICAL TREATMENT

Overactive Bladder - Pharmacological treatment

- 2 main options:

1. Antimuscarinics

2. Beta-adrenergic treatment

Bladder Physiology I

- Urinary bladder innervated by parasympathetic cholinergic nerves
- ACh contracts the detrusor smooth muscle through action at muscarinic receptors
- Contributing to emptying of the bladder
- Predominantly M3 receptor involved

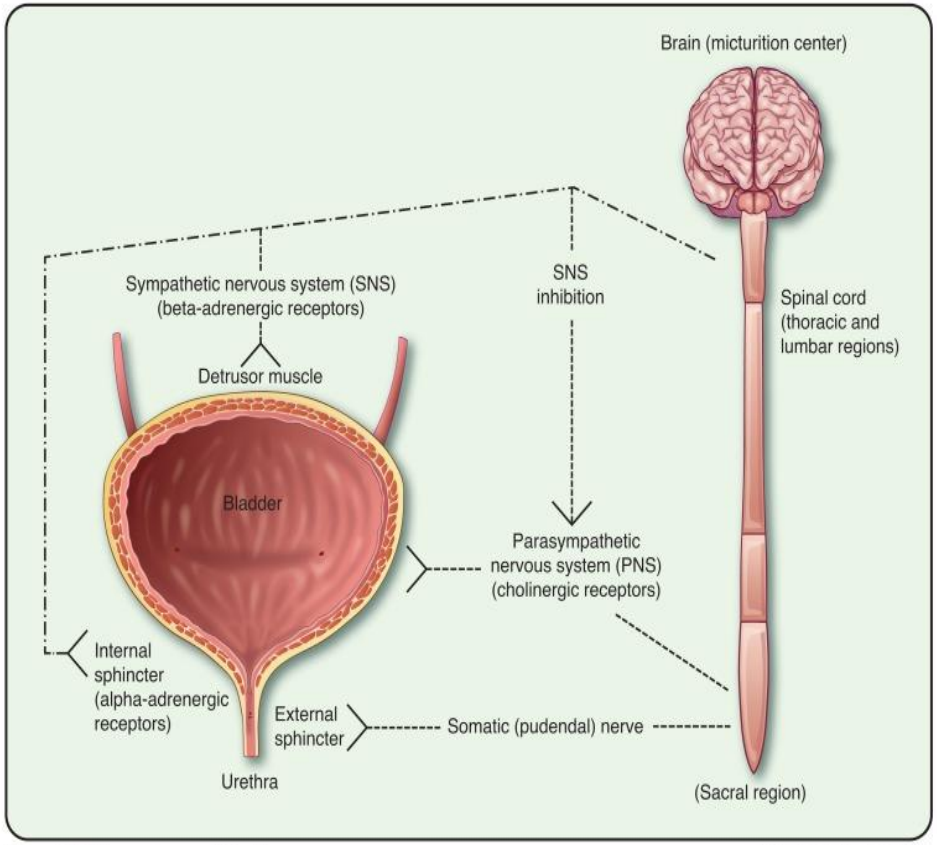


Figure 1 Bladder anatomy and physiology.

Illustration by Alison Schroeer

ROLE FOR ANTIMUSCARINICS

Bladder Physiology II

- Beta 3 adrenoceptors are predominant beta receptors expressed in SM of detrusor
- Stimulation: induces detrusor relaxation
- Resulting in relaxation of bladder, helping it to fill and to store urine

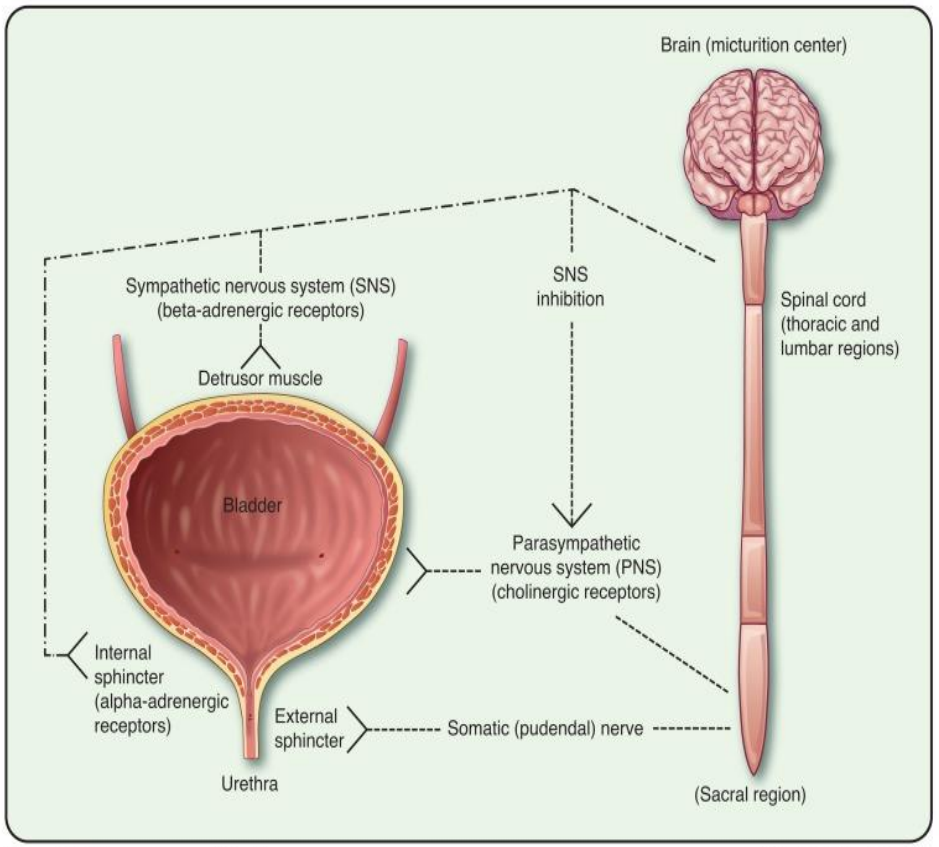


Figure 1 Bladder anatomy and physiology.

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ROLE FOR BETA AGONISTS

1. Antimuscarinics

- AKA Anticholinergics
- Inhibit binding of ACh to cholinergic receptor suppressing involuntary bladder contraction
- In addition
  - Increase urine volume at which 1st involuntary bladder contraction occurs
  - Decrease amplitude of involuntary bladder contraction
  - Increase bladder capacity
- Modest benefit over placebo

Antimuscarinics

- 7 currently licensed in Ireland
  - Tolterodine (Detrusitol®)
  - Solifenacin (Vesitirim®)
  - Fesoterodine (Toviaz®)
  - Oxybutynin (Lyrinel®, Cystrin®)
  - Trospium (Flotros®)
  - Flavoxate (Urispas®)
  - Propiverine (Detrunorm®)

HSE Medicines Management Programme:
SR TOLTERODINE the preferred drug for UI, frequency and OAB.

Performance

- Similar performance profile
- No compelling evidence of clinically meaningful superiority of one over another for treatment of UI, frequency, OAB

Toxicity

- Similar toxicity profile
- Antimuscarinics are not particularly well tolerated.
- Adherence to and persistence with antimuscarinics is generally low
  - Side effects
  - Unmet treatment expectations

- Evidence that ER preparations of antimuscarinics such as oxybutynin and tolterodine are better tolerated than IR preparations

Adverse effects

- Dry mouth
- Blurred vision
- Constipation
- Heart palpitations
- Facial flushing
- In excess, can cause urinary retention
- Drowsiness esp. in combi with alcohol, sedatives, hypnotics
- Prolongation of QT interval

Cognitive impact

- Ltd trials conducted in elderly people with UI
- Central adverse effects include delirium, confusion, exacerbation of existing memory loss
  - especially concerning in elderly

- Recommendations
  - Employ non-pharmacological tx first
  - Use with caution in those at risk of, or have, cognitive dysfunction
  - Reduce anticholinergic load
  - Monitor

Contra-indications

- Narrow-angle glaucoma
- Urinary retention
- Bowel obstruction
- Ulcerative colitis
- Myasthenia gravis
- Severe heart disease

Hepatic Metabolism

DRUG	HEPATIC METABOLISM
Oxybutynin	CYP3A4
Trospium	Ltd role of hepatic metabolism
Tolterodine	CYP3A4, CYP2D6
Solifenacin	CYP3A4
Fesoterodine	CYP3A4
Propiverine	CYP3A4

CYP 3A4: Interactions with macrolides, ketoconazole etc

CYP 2D6: Interactions with TCAs, fluoxetine

Interactions

- Anti-arrhythmics and sotalol: increased risk of ventricular arrhythmias with tolterodine

- Antibacterials
  - Dose ↓ of fesoterodine with clarithromycin
  - Avoid tolterodine with clarithromycin/erythromycin
  - Avoid rifampicin with tolterodine

- Antidepressants e.g. St Johns Wort

- Antifungals

Beta-adrenergic treatment

2.Beta-adrenergic treatment Mirabegron

- Beta 3 agonist
- Beta 3 adrenoceptors are predominant beta receptors expressed in SM of detrusor
  - Stimulation induces detrusor relaxation
- Better than placebo for improvement of UUI symptoms (no evidence better for cure)
- Clinical effectiveness similar to antimuscarinics, but different side effect profile
- No risk of QTc prolongation or raised intraocular pressure observed

Mirabegron

- Common side effects
  - UTI, tachycardia, nausea, constipation, diarrhoea, headache, dizziness
- Hepatic Metabolism: CYP3A4, CY2D6
- Discontinuation rates similar to tolterodine
  - Incidence of dry mouth significantly lower

- Contra-indications
  - × Severe uncontrolled hypertension
  - × Hypersensitivity

Mirabegron

- Dose: 50mg once daily
  - Dose reduction in renal/hepatic impairment: 25mg od

- NICE recommendations
  - Option for treating OAB only when antimuscarinics contra-indicated, clinically ineffective or unacceptable side effects

Interactions

- In mild to moderate renal impairment (GFR 30 -89 mL/min/1.73 m^2) or mild hepatic impairment & concomitantly receiving strong CYP3A inhibitors, such as itraconazole, ketoconazole, ritonavir and clarithromycin
  - Recommended dose = 25 mg od with or without food
- Antiviral – ritonavir
- Digoxin
- Dabigatran

Oestrogen Therapy

- Vaginal oestrogen therapy may improve or cure UI in post-menopausal women
- No evidence that non-vaginal route of oestrogen confers any improvement in UI

- Recommendations
  - Offer intravaginal oestrogens for the treatment of OAB symptoms in postmenopausal women with vaginal atrophy (NICE 2006)

Desmopressin

- Synthetic analogue of vasopressin (Antidiuretic Hormone)
- Oral, nasal, injection
- Nocte to treat nocturnal enuresis

Desmopressin

- Desmopressin may be considered specifically to reduce nocturia in women with UI or OAB who find it a troublesome symptom.
  - Use particular caution in women with cystic fibrosis and avoid in those over 65years with cardiovascular disease or hypertension.

[NICE 2006, amended 2013]

  - BNF: 25mcg 1 hour before bedtime (BNF)
- Idiopathic nocturnal enuresis in males
  - 50mcg 1 hour before bedtime

OAB Treatment

- Before starting pharmacological treatment discuss

  - Likelihood of success
  - Common adverse effects
  - Frequency and route of administration
  - Some adverse effects such as dry mouth and constipation may indicate that treatment is starting to have an effect
  - May not see the full benefits until they have been taking the treatment for 4 weeks.
  - Long term effects of anticholinergics for OAB on cognitive function are unclear

(NICE 2019)

Botulinum toxin type A injection

- Offer bladder wall botulinum toxin type A to women with OAB caused by detrusor overactivity that has not responded to non-surgical management, including pharmacological treatments [NICE 2019]

Stress urinary incontinence

Stress UI – Pharmacological Treatment

- Focused on effect of alpha-adrenoceptors in increasing closure urethral pressure in women
- Bladder neck and proximal urethra have many alpha receptors
- Activation leads to increase in smooth muscle (SM) tone
- E.g. duloxetine

Duloxetine

- Inhibits presynaptic re-uptake of neurotransmitters 5-HT and Noradrenaline (SNRI)

- In sacral spinal cord - ↑conc of 5HT and NA in synaptic cleft increases urethral tone during the storage phase of the micturition cycle.

Duloxetine

- Does not cure UI
- Can improve SUI/MUI in women

- Significant side effects (GI, CNS) leading to high rate of treatment discontinuation
  - Nausea & vomiting (40% in 1 trial)
  - Dry mouth, constipation, dizziness, insomnia, somnolence and fatigue, hyperhidrosis
  - ↑ in BP
  - Hypernatraemia
  - Bleeding abnormalities
  - Suicidal thoughts

Duloxetine (Yentreve®)

- Licensed for women for the treatment of moderate to severe SUI
- 40 mg twice daily
  - Reassess after 2-4 weeks of treatment (evaluate benefit and tolerability)
  - Dose titration: initiate at 20mg bd, may decrease (not eliminate), the risk of nausea and dizziness.
- Hepatic Metabolism: CYP1A2, CYP2D6

Contra-indications

- Hepatic impairment
- Concomitant use with non-selective, irreversible MAOI
- Concomitant use with CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin, or enoxacin)
- Severe renal impairment (creatinine clearance <30 ml/min)
- Not to be initiated in patients with uncontrolled hypertension – potential risk of hypertensive crisis
- Hypersensitivity

Cautions

- Mania & seizures
- Serotonin syndrome
- Mydriasis
- Blood pressure/HR
- Renal impairment
- Haemorrhage
- Withdrawal symptoms
- Hyponatraemia
- Depression
- Suicidal ideation/behaviour
- Hepatitis
- Akathesia

Interactions

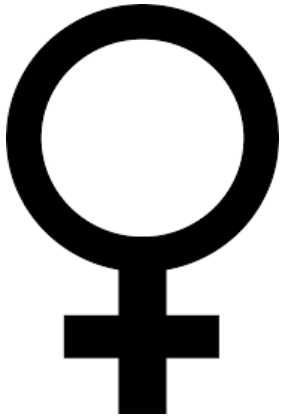
- MAOIs
- CYP1A2 inhibitors e.g. fluvoxamine
- CNS medicinal products e.g. alcohol/sedatives
- Serotonergic Agents
- Anticoagulants/antiplatelets
- Smoking

Recommendations

- NICE

  Do not use duloxetine as first-line treatment for **women** with predominant stress UI. Do not routinely offer duloxetine as a second-line treatment for women with stress UI, although it may be offered as second-line therapy if women prefer pharmacological to surgical treatment or are not suitable for surgical treatment.

  If duloxetine is prescribed, counsel women about its adverse effects.[2006]



Duloxetine in **men**

- Duloxetine has also been evaluated as a potential treatment option for men with SUI after radical prostatectomy. The drug reduced incontinence episodes and improved quality of life.

UI in men associated with benign prostatic hyperplasia (BPH)

Pharmacologic treatment
UI in men associated with BPH

1. Alpha blockers

2. 5-alpha reductase inhibitor

Offer drug treatment only to men with bothersome LUTS when conservative management options have been unsuccessful or are not appropriate. [NICE 2010]

Pharmacologic treatment
1. Alpha blockers

- Alpha blockers
  - Relax smooth muscle of bladder neck and prostate
  - Increase urine flow rate
  - Reduce symptoms due to obstruction
  - Generally well tolerated
  - E.g. Tamsulosin, alfuzosin, silodosin, doxazosin, terazosin

Offer an alpha blocker (alfuzosin, doxazosin, tamsulosin or terazosin) to men with moderate to severe LUTS. [NICE 2010]

Adverse effects of Alpha Blockers

- CV system
  - Orthostatic hypotension, dizziness, syncope, tachycardia, palpitations
- GI
  - GI disturbances, dry mouth
- CNS
  - Somnolence, headache, blurred vision
- Also erectile dysfunction, rhinitis
- 1st dose hypotension

Contraindications and Cautions- Alpha Blockers

- Avoid in patients with history of
  - Postural hypotension
  - Micturition syncope
- Patients taking anti-hypertensives may require lower doses and specialist supervision
- Caution in elderly
- Caution if undergoing cataract surgery
  - Risk of floppy iris syndrome

Alpha Blocker	Renal Impairment	Hepatic Impairment	HF and Angina
Tamsulosin	Caution CrCl <10mls/min	Avoid in severe	
Alfuzosin	Avoid MR products if eGFR <30mls/min	Avoid in severe	Discontinue if angina worsens. Caution in Acute HF, history of QT prolongation
Silodosin	Not recommended if CrCl <30mls/min	Avoid in severe	Caution in HF
Doxazosin	No dose adjustment	Caution Avoid in severe	Caution in HF
Terazosin	No dose adjustment	Caution	CI in CHF due to mechanical obstruction

Interactions
Alpha blockers

- Potentially clinically significant:
  - MAOIs, antifungals, antivirals, beta-blockers, calcium channel blockers, diuretics, moxisylyte, H2 antagonists
- PDE5 inhibitors
  - Concurrent use increases risk of hypotension
  - Only use when alpha blocker therapy stabilised
  - Sildenafil: separate from alpha blockers by 4 hours
  - Vardenafil: separate from alpha blockers by 6 hours (except tamsulosin and alfuzosin)
  - Tadalafil and doxazosin contra-indicated

2. 5-alpha reductase inhibitors

- 2 currently available
  - Dutasteride (Avodart®)
  - Finasteride (Proscar®)

- Mechanism of action
  - Competitively block the enzyme 5-alpha reductase inhibiting conversion of testosterone to dihydrotestosterone
  - Resulting in epithelial atrophy and reduction of prostate volume of up 25%

  - Note: Above only useful for LUTS 2° to BPH only in the presence of prostate enlargement

Current guidelines: 5-alpha reductase inhibitor

- Offer a 5-alpha reductase inhibitor to men with LUTS who have prostates estimated to be larger than 30 g or a PSA level greater than 1.4 ng/ml, and who are considered to be at high risk of progression (for example, older men). [NICE 2010]

- Consider offering a combination of an alpha blocker and a 5-alpha reductase inhibitor to men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30 g or a PSA level greater than 1.4 ng/ml. [NICE 2010]

Contraindications and Cautions 5-alpha reductase inhibitor

- **Dutasteride**
- Contra-indications
  - Hypersensitivity to soya, peanut, or any of the other excipients.
  - Severe liver disease.
- Cautions
  - Mild to moderate liver disease
- Drug interactions
  - CYP3A4 interactions

- **Finasteride**
- Contra-indications
  - People with hypersensitivity to any of the excipients.
  - No data on finasteride in liver disease. Reasonable approach would be to use it in the same way as dutasteride as both drugs eliminated mainly by hepatic metabolism

Drugs contributing to incontinence

- Diuretics
- Caffeine
- Anticholinergics
- Psychotropics – antipsychotics, antidepressants, sedatives, hypnotics, CNS depressants
- Narcotic analgesics
- Alpha adrenergic blockers/agonists
- Beta-adrenergic agonists, CCB, alcohol

References

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  - LUTS in men; Urinary incontinence in women
- www.medicines.ie
- Overactive bladder: strategies to ensure treatment compliance and adherence. Clinical Interventions in Aging June 2016