Drug Therapies for Urinary Disorders

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Introduction and definitions

Urinary incontinence (UI), defined as involuntary loss of urine, is a common health condition that affects women of all ages, with a wide range of clinical presentation and severity. The rate in adult women is variously reported as 12% to 55%. Although rarely life-threatening, UI may seriously influence the physical, psychological and social wellbeing of affected women and is associated with profound impact on their quality of life.

The International Continence Society classifies lower urinary tract dysfunction as Lower Urinary Tract Symptoms (LUTS) and Urodynamic Diagnosis. LUTS are divided into storage symptoms and voiding symptoms. Urinary incontinence is a storage symptom and is defined as "the complaint of any involuntary loss of urine".

UI may be further defined according to the patient's symptoms:

- Urgency Urinary Incontinence: involuntary leakage accompanied by or immediately preceded by urgency
- Stress Urinary Incontinence (SUI): involuntary leakage on effort or exertion, or on sneezing or coughing
- Mixed Urinary Incontinence: involuntary leakage associated with urgency and also with effort, exertion, sneezing and coughing
- Nocturnal Enuresis: any involuntary loss of urine occurring during sleep
- Post-micturition dribble and continuous urinary leakage: denotes other symptomatic forms of incontinence
- Overactive bladder (OAB) is characterized by the storage symptoms of urgency with or without urgency incontinence, usually with frequency and nocturia.

Urodynamic diagnosis:

- Detrusor Overactivity (DO): characterized by involuntary detrusor contractions during the filling phase, this may be spontaneous (idiopathic) or provoked (neurogenic)
- Urodynamic stress incontinence is noted during filling cystometry, and is defined as the involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction

For women with stress, urgency or mixed urinary incontinence, conservative management (non-pharmacological and pharmacological), and is usually advocated as an initial intervention since it carries minimal risks. Non-pharmacological methods include lifestyle interventions like caffeine reduction, modification of fluid intake and weight loss, physical therapy with supervised pelvic floor muscle training, and behavioral therapies like bladder training and timed voiding. Pharmacological treatment includes various groups of drugs; this article outlines several classes of drugs and important evidence-based effective treatments.

Table 1a: Drugs used in the treatment of OAB/ DO

DRUG	Level of Evidence*	Grade of recommendation ^
Antimuscarinic drugs		
Tolterodine, Trospium, Solifenacin and Darifenacin	1	A
Propantheline	2	B
Atropine, hyoscyamine	3	C
Drugs acting on membrane channels		
Calcium antagonists and K-Channel openers	2	D
Drugs with mixed actions		
Oxybutynin and Propiverine	1	A
Flavoxate	2	D
Antidepressants		
Imipramine (TCA)	3	C
Duloxetine (SSRI)	2	C
Alpha adrenergic receptor antagonists		
Alfuzosin, Doxazosin, Prazosin	3	C
Beta adrenergic receptor antagonists		
Terbutaline, Salbutamol	3	C
COX-inhibitors		
Indomethacin, Flurbiprofen	2	C
Hormones		
Estrogen	2	C
Desmopressin	1	A

(Modified from Andersson KE 2009, ICS)

Table 1b: Drugs used in the treatment of SUI

Duloxetine	1	B
Imipramine	3	D
Methoxamine	2	D
Ephedrine, Norephedrine (phenylpropanolamine)	3	D
Estrogen	2	D

(Modified from Andersson KE 2009, ICS)

* Levels of evidence: Level 1: Systematic reviews, meta-analyses, good uality randomized controlled clinical trials (RCTs) Level 2: RCTs , good quality prospective cohort studies Level 3: Case-control studies, case series Level 4: Expert opinion

^ Grades of recommendation Grade A: Based on level 1 evidence (highly recommended) Grade B: Consistent level 2 or 3 evidence (recommended) Grade C: Level 4 studies or "majority evidence" (optional) Grade D: Evidence inconsistent/inconclusive (no recommendation possible) or the evidence indicates that the drug should not be recommended

DRUGS FOR OVERACTIVE BLADDER / DETRUSOR OVERACTIVITY (Refer Table 1A)

1. Antimuscarinic (anticholinergic) drugs

Anticholinergics are the first-line agents used to treat urge incontinence and OAB. They inhibit the binding of acetylcholine to the muscarinic receptor in the detrusor, thereby suppressing involuntary bladder contractions of any etiology. They increase the urine volume at which first involuntary bladder contraction occurs, decrease the amplitude of the involuntary bladder contraction, and may increase bladder capacity; hence they decrease micturition frequency and sensation of urgency.

All anticholinergic drugs have a similar performance profile and toxicity, and potential adverse effects include blurred vision, dry mouth, heart palpitations, drowsiness, and facial flushing. When anticholinergic drugs are used in excess, the bladder may go into acute urinary retention. All these drugs are contraindicated in patients with narrow-angle glaucoma, bowel obstruction, ulcerative colitis, myasthenia gravis, and severe heart diseases. Because of the potential for drowsiness, especially when combined with alcohol, sedatives, or hypnotic drugs, these agents may impair the patient's ability to drive or operate machinery.

Atropine Sulphate

Atropine (dl-hyoscyamine) is rarely used for treatment of OAB/ DO because of its systemic side effects, which preclude its oral use. However, in patients with neurogenic DO, intravesical atropine may be effective for increasing bladder capacity without causing any systemic adverse effects

Propantheline Bromide

It is a quaternary ammonium compound, non-selective for muscarinic receptor subtypes and has a low (5 to 10%) and varying biological availability. It is usually given in a dose of 15 to 30 mg 4 times daily, but to obtain an optimal effect, individual titration of the dose is necessary, and often higher dosages are required.

Tolterodine tartrate

Tolterodine is a nonspecific competitive muscarinic receptor antagonist for OAB. However, it differs from other anticholinergic types in that it has selectivity for urinary bladder over salivary glands. Tolterodine exhibits a high specificity for muscarinic receptors. It has minimal affinity for other neurotransmitter receptors and other potential targets, such as calcium channels. It is available as immediate release 2 mg tablet twice daily and extended release 4 mg once daily, which has been shown to have better efficacy and tolerability. Several randomised, double blind, placebo-controlled studies on patients with OAB/DO using Tolterodine have documented a significant reduction in micturition frequency and number of incontinence episodes; the mean decrease in urge incontinence episodes and urinary frequency was 50% and 17% respectively.

Trospium chloride

Trospium is a nonspecific quaternary ammonium compound that is excreted intact in the urine and thus is not dependent on the cytochrome P450 system for its metabolism. Being a quarternary amine, it is less likely to penetrate the blood-brain barrier. It antagonizes acetylcholine's effect on muscarinic receptors. Its parasympathetic effect reduces smooth-muscle tone in the bladder. It is available as 20mg twice daily tablet as well as an extended release formulation.

Darifenacin hydrobromide

Darifenacin is an extended-release product that elicits competitive muscarinic receptor antagonistic activity. It has high affinity for the M3 receptors and less affinity for other muscarinic receptors. Hence it reduces bladder smooth-muscle contractions along with reduction of the adverse events related to the blockade of other muscarinic receptor subtypes. Darifenacin has been developed as a controlled release formulation, which allows once-daily dosing. Recommended dosages are 7.5 and 15 mg per

day. It should be swallowed whole, and not chewed or crushed. Its clinical effectiveness has been documented in several RCTs.

Solifenacin succinate

Solifenacin is a newer competitive muscarinic-receptor antagonist for the treatment of OAB with symptoms of urge incontinence, urgency, and urinary frequency. It shares a similar muscarinic receptor affinity as oxybutyinin and is available in 2 doses, 5mg and 10mg daily. Like Darifenacin, it should be swallowed whole and not crushed or chewed.

Fesoterodine fumarate

Fesoterodine is the most recent anticholinergic agent to be approved. It is available in 2 doses, 4mg and 8mg daily; the 8mg dose has been shown to be superior to tolterodine in the reduction of urge incontinence episodes. It shares a similar muscarinic receptor affinity as tolterodine.

2. Drugs acting on membrane channels

Calcium channels play an important role in the regulation of free intracellular calcium concentrations and contribute to the regulation of smooth muscle tone. Two major groups of calcium channels are the voltage-gated and store-operated channels; the latter are relatively unimportant while the former have been implicated in the regulation of bladder smooth muscle tone. However at present, there is no clinical evidence to support the possible use of calcium antagonists like Verapamil in the treatment of bladder dysfunction. In a similar fashion to calcium channels, potassium channels also contribute to the membrane potential of smooth muscle cells and hence to the regulation of smooth muscle tone. However despite promising preclinical efficacy data, potassium channel openers at present are not a therapeutic option due to a lack of selectivity for bladder tissues.

3. Drugs with mixed action

Some drugs used to block DO have been shown to have more than one mechanism of action. They all have a more or less pronounced antimuscarinic effect and, in addition, an often poorly defined “direct” action on bladder muscle.

Oxybutinin

Oxybutynin has an anticholinergic and a direct smooth muscle relaxant effect on the urinary bladder, along with local anesthetic effect on the irritable bladder. The human detrusor has M2 and M3 muscarinic receptors. The M3 receptor mediates contractile response of human detrusor. Oxybutynin has greater affinity for the M3 receptor. Urodynamic studies have shown oxybutynin increases bladder size, decreases frequency of symptoms, and delays initial desire to void.

Oxybutinin is available as immediate release, extended release and transdermal forms. Immediate release oxybutynin 7.5mg to 15mg is recognized for its efficacy and most of the newer anti-muscarinic agents have been compared to it; the advantage of the newer formulations lies in improved dosing schedules and side-effect profile. An extended release oxybutynin 10mg once daily oral formulation avoids first pass metabolism in liver and upper gastrointestinal tract to avoid cytochrome P450 enzymes. It has excellent efficacy, with minimal adverse effects. Oxybutynin transdermal delivery system offers a twice-weekly dosing regimen and the potential for improved patient compliance and tolerability.

Flavoxate

Flavoxate is used for symptomatic relief of dysuria, urgency, nocturia, and incontinence, as may occur in cystitis, urethritis, and urethrocystitis/ urethrotrigonitis. It exerts a direct relaxant effect on smooth muscles via phosphodiesterase inhibition. It is given in the dose of 200mg three times a day and provides relief for a variety of smooth muscle spasms.

4. Antidepressants

Tricyclic Antidepressants (TCAs):

Historically, these drugs were used to treat major depression; however, TCAs have an additional use in the treatment of bladder dysfunction. They increase norepinephrine and serotonin levels and also exhibit anticholinergic and direct muscle relaxant effect on the bladder.

Imipramine hydrochloride

Imipramine facilitates urine storage by decreasing bladder contractility and increasing outlet resistance. It has an alpha-adrenergic effect on the bladder neck and an antispasmodic effect on the detrusor muscle. Imipramine also has a local anesthetic effect on bladder mucosa. Very few studies have been performed during the last decade to assess the risks and benefits of imipramine in voiding disorders. No good quality RCTs have documented that the drug is effective in the treatment OAB. However, a beneficial effect has been documented in the treatment of nocturnal enuresis. The usual dose is 75mg daily at night.

Amitriptyline hydrochloride

A TCA with sedative properties, amitriptyline increases the circulating levels of norepinephrine and serotonin by blocking their reuptake at nerve endings. It is ineffective for use in urge incontinence but is extremely effective in decreasing symptoms of urinary frequency in women with pelvic floor muscle dysfunction. Amitriptyline restores serotonin levels and helps break the cycle of pelvic floor muscle spasms. It is well tolerated and effective in the majority of women with urinary frequency.

Selective Serotonin Reuptake Inhibitor (SSRI):

Duloxetine

It is a combined noradrenaline and serotonin reuptake inhibitor, which has been shown to significantly increase sphincteric muscle activity during the filling/storage phase of micturition. The dose is 40 to 80mg daily. Common side effects include nausea, dry mouth, dizziness, constipation, insomnia and fatigue

5. Hormones

Hormones are used to treat OAB in association with atrophic urethritis and are not recommended as first-line therapies.

Estrogen

Combined hormone therapy and unopposed estrogen therapy have been found to increase the incidence of urinary incontinence in women without symptoms at baseline; women receiving estrogen therapy should be counseled that incontinence symptoms may worsen. In initially symptomatic women, urinary frequency increased with both treatments. Smaller studies examining the use of oral estrogen preparations in the treatment of stress or urge incontinence found that the use of estrogen did not reduce incontinence. Therefore, oral estrogen therapy is not recommended for treatment or prevention of any type of urinary incontinence.

There is good evidence that low-dose (local) vaginal estrogen therapy may be effective in OAB as it reverses the symptoms and cytological changes of urogenital atrophy. The reason for this is that the symptoms of urinary urgency, frequency and urge incontinence may be a manifestation of urogenital atrophy in older post menopausal women rather than a direct effect on the lower urinary tract. Whilst there is good evidence that the symptoms and cytological changes of urogenital atrophy may be reversed by low dose (local) vaginal estrogen therapy there is currently no evidence that estrogens with or without progestogens should be used in the treatment of urinary incontinence.

Desmopressin

The endogenous hormone vasopressin (also known as anti-diuretic hormone) can contract vascular smooth muscle and stimulate water reabsorption in the renal medulla. These functions are mediated by specific vasopressin receptors of which two major subtypes exist, the V1 and the V2 receptors of which the V2 subtype is particularly important for the anti-diuretic effects of vasopressin. While it remains largely unknown in which fraction of patients nocturia can indeed be explained by too little vasopressin, the presence of nocturnal polyuria in the absence of behavioural factors explaining it is usually considered as an indication that a lack of vasopressin may exist. Based upon this, vasopressin receptor agonists have been explored for the treatment of nocturia and OAB. Oral desmopressin at doses of 0.1-0.4 mg was found to be well tolerated and resulted in a significant improvement in UI compared to placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. Quality of life also improved. However, hyponatremia is one of the main, clinically important, side-effects of administration and can lead to a range of adverse events from mild headache, anorexia, nausea, and vomiting to loss of consciousness, seizures, and death.

DRUGS FOR SUI (Refer Table 1B)

1. Alpha adrenoceptor agonists

The bladder neck contains a high concentration of receptors that are sensitive to alpha-agonists. Alpha-agonists increase bladder outlet resistance by contracting the bladder neck and hence are beneficial in the treatment of mild to moderately severe stress incontinence in women. Several drugs with agonistic effects on alpha- agonists have been used in the treatment of SUI. However, ephedrine and norephedrine (phenylpropanolamine; PPA 50mg twice daily) have been the most widely used.

Pseudoephedrine hydrochloride

Pseudoephedrine helps stress incontinence. The subjective improvement and cure rates are similar to that of phenylpropanolamine. Pseudoephedrine stimulates vasoconstriction by directly activating alpha-adrenergic receptors.

Phenylpropanolamine

Epinephrine stores are released under phenylpropanolamine stimulation and produce alpha- and beta-adrenergic stimulation. These effects may increase bladder outlet resistance.

2. SSRIs

Duloxetine, as mentioned earlier, is a potent inhibitor of neuronal serotonin and norepinephrine reuptake. Its antidepressive action is theorized to be due to serotonergic and noradrenergic potentiation in the CNS. Duloxetine is licensed at 40 mg twice daily for the treatment of SUI in Europe for women with moderate to severe incontinence (defined as 14 or more episodes per week). In the USA it is not approved for SUI but for the treatment of major depressive disorder (20-30 mg twice daily). In India it is available as 30mg and 60mg tablets.

3. Estrogens

Post -menopausal women with stress urinary incontinence should be offered a trial of topical estrogen therapy with appropriate safeguards to its use, as mentioned earlier.

4. Botulinum Toxins

Intradetrusor injections with botulinum toxin are a novel treatment modality shown to decrease episodes of urinary leakage in patients who have failed pharmacological therapy. Intramural bulking agents should be considered for the management of SUI if conservative management has failed. Description of these agents is beyond the scope of this article.

Other drugs which have poor levels of evidence and grades of recommendation have not been described in detail.

FUTURE DIRECTIONS:

Peripherally acting drugs like Vitamin D3 receptor analogues and centrally acting drugs like GnRH, Gabapentin, Tramadol and Neurokinin A and its NK1-receptor antagonist have been demonstrated in various CNS regions, including those involved in micturition control. Ongoing research is exciting and promises to improve our understanding and management of incontinence.

SUMMARY OF RECOMMENDATIONS

- Immediate release oxybutynin should be offered to women with OAB or mixed UI as first-line drug treatment if bladder training has been ineffective. If immediate release oxybutynin is not well tolerated, darifenacin, solifenacin, tolterodine, trospium, or an extended release or transdermal formulation of oxybutynin should be considered as alternatives. Women should be counselled about the adverse effects of antimuscarinic drugs.
- Flavoxate, propantheline and imipramine should not be used for the treatment of UI or OAB in women.
- Duloxetine is not recommended as a first-line treatment for women with predominant SUI and should not be used as a cure for stress incontinence.
- Duloxetine should not routinely be used as a second-line treatment for women with SUI, although it may be offered as second-line therapy in women whose priority is symptom-reduction, not cure and who prefer pharmacological to surgical treatment or are not suitable for surgical treatment. Counseling concerning side-effects, particularly nausea should be done.
- Systemic hormone replacement therapy is not recommended for the treatment of UI.
- Intravaginal estrogens are recommended for the treatment of OAB symptoms in postmenopausal women with vaginal atrophy.

(Modified from ACOG Guidelines 2005 and NICE Guidelines 2006)

References and further reading

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