Systematic review of overactive bladder therapy in females

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Abstract

Although the prevalence of overactive bladder (OAB) is similar in both male and female populations, females have a greater tendency to seek medical advice regarding their symptoms. A review of the evidence of therapy among women shows that a variety of modalities has been shown to be effective for symptom improvement in women with OAB. Bladder retraining/re-education should be considered for all women with OAB. With respect to first-line pharmacotherapy with antimuscarinic agents, the development of extended release preparations, bladder selective M3 antagonists and alternative routes of delivery, have improved compliance and persistence. Other pharmacotherapeutic options with potential for providing benefit include antidepressants, vasopressin analogues, alpha-adrenoceptor antagonists and beta-adrenoceptor agonists. There are also a number of newer agents currently being investigated, including calcium channel blocking agents, potassium channel opening drugs, beta agonists and neurokinin receptor antagonists. Intravesical injections of botulinum toxin may be an alternative, while surgery can be considered for truly intractable cases.

Overactive bladder (OAB) is a common, troublesome and often under diagnosed condition that significantly affects quality of life. Studies have suggested that there could be 17.5 million women in the United States who suffer from the condition.[1] The prevalence of OAB is similar in both male and female populations and increases with age.[2] Females, however, have a greater tendency to seek advice regarding their symptoms.

The following review will present the various treatment options available to women with OAB and provide key highlights from the evidence base for those treatments. Therapy ranges from conservative measures such as bladder retraining through medication and, occasionally, reconstructive surgery.

Conservative measures

Lifestyle advice

Lifestyle advice is important for all OAB sufferers. Decreasing fluid intake by 25% has been shown to be associated with significant reductions in urgency, frequency and nocturia, while increasing fluid intake worsened frequency.[3]

Reducing caffeine intake is another lifestyle intervention that can be helpful. High caffeine intake is an independent risk factor for detrusor overactivity, and the relationship may be dose dependent.[4] With respect to the specific types of drinks consumed, tea drinking (but not coffee) has been epidemiologically associated with all forms of incontinence.[5] Diet soft drinks have also been found to be associated with a higher rate of urgency and frequency than regular soft drinks or carbonated water.[6]

Weight loss has also been found to decrease incontinence in moderately and morbidly obese women.[7]

Bladder retraining

Bladder retraining should be considered for all women with OAB. Pelvic floor muscle training may be effective in those with mixed or urgency incontinence.[7] Bladder re-education may include biofeedback and bladder drill. In a retrospective observational study of 114 women undergoing inpatient bladder retraining, the investigators found that bladder retraining was associated with a statistically significant decrease in frequency of incontinence episodes and nocturia.[8] Furthermore, there was also an increase in the interval between voids. Twenty-three percent were cured of their symptoms, 36% reported improvement and 27% did not find any change (Fig. 1).

Pharmacotherapy

A wide variety of pharmacologic therapy is employed in OAB. Most of the drugs have an antimuscarinic effect, but antidepressants, vasopressin analogues and alpha-adrenoceptor antagonists, beta-adrenoceptor agonists are also used.

Antimuscarinics

These are the most commonly used agents for OAB. They work by reducing intra-vesical pressure, increasing compliance, raising the volume threshold for micturition and reducing uninhibited detrusor contractions.[9]

For many years, the antimuscarinics (oxybutynin, tolterodine, propiverine and trospium) were available only in immediate-release formulations. The major shortcoming of all these drugs was a high burden of antimuscarinic side effects (e.g., dry mouth, constipation). These side effects, coupled with insufficient efficacy, led to a very low rate of persistence with these medications in the longer term.[10]

With the subsequent development and use of sustained-release formulations, persistence rates improved somewhat, but were still far from optimal. In a study examining persistence to extended-release agents (oxybutynin or tolterodine), only 44% of those taking a long-acting agent remained adherent past 30 days.[11] Other methods that can be used in an effort to improve persistence are the use of more selective M3 antagonists (e.g., solifenacin, darifenacin, fesoterodine) and alternative routes of delivery of oxybutynin (e.g., patch, gel, intravaginal ring).

Choosing a particular antimuscarinic for the treatment of OAB in women involves attempting to determine the best match of agent characteristics with those of the patient. The key advantages and disadvantages of each antimuscarinic agent are shown in Table 1.

Desmopressin

Desmopressin has been used for many years for the treatment of nocturia and nocturnal enuresis in children[12] and adults.[13] There is also evidence of modest efficacy for the treatment of OAB. A proof-of-concept, double-blind, placebo-controlled, randomized, cross-over study included 88 adult patients with OAB.[14] The investigators reported that treatment with desmopressin 0.2 mg was associated with a significant reduction in the number of voids over eight hours (3.2 vs. 4.2; $p < 0.001$). There was also a significant increase in the time to first urgency episode and a decrease in the number of urgency episodes for desmopressin compared to placebo ($p < 0.003$).

The major side effect of concern with desmopressin is hyponatremia, although no episodes were recorded in the clinical trial in OAB.

Estrogens

The evidence for adding estrogen in combination with an antimuscarinic drug is equivocal. One study evaluating the combination of tolterodine and conjugated equine estrogen cream reported that the combination was associated with significant improvements in daytime frequency and voided volume (but not nocturia, urgency or urgency incontinence) compared to tolterodine alone.[15]

The investigators of another study, which evaluated tolterodine with or without oestriol cream, reported that there was no difference between arms in any of the efficacy endpoints.[16] Subjects all had detrusor overactivity rather than just symptoms of OAB.

Antidepressants

Although these agents are sometimes used for the treatment of OAB, they are not approved for this indication, nor is there any clinical trial evidence supporting this use.

Future directions in pharmacotherapy

Newer agents in different classes are under evaluation including calcium channel blocking agents, potassium channel opening drugs, beta agonists and neurokinin receptor antagonists. Combination therapies including an antimuscarinic and an agent with a complementary mechanism of action, are also under investigation.

Other therapies

Approximately 10% of patients will continue to suffer from distressing lower urinary tract symptoms despite conservative measures and pharmacologic therapy. More invasive strategies can be considered for these patients.

Botulinum toxin

Evidence suggests that intravesical injections of botulinum toxin may offer an alternative, albeit temporary, measure in women with intractable detrusor overactivity.[17-19] It should be noted that intermittent self-catheterization may be required in a minority (~25%) of patients treated with botulinum toxin.

Neuromodulation

Both peripheral posterior tibial nerve stimulation[20,21] and sacral neuromodulation[22,23] are also alternative therapeutic options, although less cost effective than antimuscarinics.[24]

Table 1. Advantages and disadvantages of antimuscarinic drugs for overactive bladder

Antimuscarinic	Advantages	Disadvantages
Oxybutynin IR	Flexible dosing, rapid onset of action, cheap	Persistence limited by dry mouth
Oxybutynin ER	Very flexible dosing	Cognitive impairment
Oxybutynin TDS	Placebo rate of systemic side effects	15-20% rate of pruritis
Oxybutynin Gel	Lower skin reactions	Acceptability?
Tolterodine ER	Well tolerated	Single dose
Solifenacin	Superior efficacy to tolterodine ER	High rate of dry mouth at 10 mg
Darifenacin	Low rate of cognitive impairment	High rate of constipation
Trospium	Does not cross blood brain barrier	ER – Recently launched in the United Kingdom, single dose
Propiverine	Well tolerated	Efficacious only for frequency
Fesoterodine	Flexible dosing	High rate of dry mouth at 8 mg

IR: immediate release; ER: extended release; TDS: transdermal system.

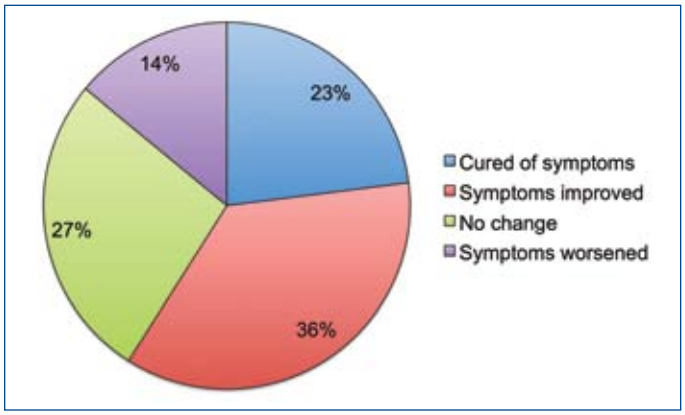

Fig. 1. Impact of bladder training: retrospective study.

Surgery

A variety of surgical augmentation techniques have been developed, including clam cystoplasty but these should only be considered in women who have failed all other treatments.

Conclusions

For the management of OAB in women, conservative therapy is indicated as primary treatment. Antimuscarinic agents are the most commonly used drugs, but their effectiveness use is limited by tolerability and efficacy (and the correspondingly low rates of compliance and persistence). Newer bladder specific antimuscarinics may offer advantages. At the moment, other options for pharmacotherapy remain under development.

Neuromodulation and botulinum toxin may be useful in patients with intractable overactive bladder, while reconstructive surgery should only be considered in those women who have failed other treatments.

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