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No. 283-Treatments for Overactive Bladder: Focus on Pharmacotherapy

This clinical practice guideline has been prepared by the Urogynaecology Committee,* reviewed by Family Practice Advisory Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Key Words: Anticholinergic, overactive bladder, urinary incontinence

Abstract

Objective: To provide guidelines for pharmacotherapy to treat overactive bladder syndrome (OAB).

Options: Pharmacotherapy for OAB includes anticholinergic (antimuscarinic) drugs and vaginal estrogen. Both oral and transdermal anticholinergic preparations are available.

Outcomes: To provide understanding of current available evidence concerning safety and clinical efficacy of pharmacotherapy for OAB; to guide selection of anticholinergic therapy based on individual patient characteristics.

Evidence: The Cochrane Library and Medline were searched for articles published from 1950 to the present related to individual anticholinergic drugs. Review articles on management of refractory OAB were also examined. Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date or language restrictions. Searches were updated on a regular basis and incorporated in the guideline to 2010.

Values: The quality of evidence is rated and recommendations are made using the criteria described by the Canadian Task Force on Preventive Health Care (Table 1).

Benefits, harms, and costs: Anticholinergics are the mainstay of pharmacotherapy for OAB. Evidence for their efficacy is mostly derived from short-term phase III randomized drug trials. Placebo response is strong, and long-term follow-up and patient subjective outcome data are lacking. Care providers need to be well acquainted with the side effects of anticholinergics and select therapy based on individual patient parameters.

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Recommendations:

1. Behavioural management protocols and functional electrical stimulation should be offered in the spectrum of effective primary treatments for overactive bladder syndrome (I-A).
2. Oral oxybutynin, immediate and extended release, as well as transdermal oxybutynin, may be offered as treatment for overactive bladder syndrome, as they are associated with significant objective clinical improvement at 12 weeks (I-A). Oxybutynin immediate release has superior cost-effectiveness but more side effects than other anticholinergics (I-A). Adverse events associated with transdermal oxybutynin are fewer than with oral oxybutynin (I-A).
3. Tolterodine, immediate and extended release, may be offered as treatment for overactive bladder syndrome, as it is associated with significant objective clinical improvement at 12 weeks (I-A).
4. Trospium, immediate and extended release, may be offered as treatment for overactive bladder syndrome as it is associated with significant clinical improvement at 12 weeks (I-A). Trospium is an adequate anticholinergic choice for overactive bladder syndrome patients with pre-existing cognitive impairment (II-B) and for overactive bladder syndrome patients taking concurrent CYP450 inhibitors (III-B).
5. Solifenacin may be offered as treatment for overactive bladder syndrome, as it is associated with significant objective clinical improvement at 12 weeks (I-A). Solifenacin may be an adequate anticholinergic choice for elderly overactive bladder syndrome patients or patients with pre-existing cognitive dysfunction (I-B).
6. Darifenacin may be offered as treatment for overactive bladder syndrome, as it is associated with significant objective clinical improvement at 12 weeks (I-A). Darifenacin is an adequate anticholinergic choice for overactive bladder syndrome patients with pre-existing cardiac concerns or cognitive dysfunction (I-B).
7. Overactive bladder syndrome patients should be offered a choice between bladder training, functional electric stimulation, and anticholinergic therapy, as there is no difference in cure rates. Combination therapy does not have a clear advantage over one therapy alone (I-A).
8. The choice of anticholinergic therapy should be guided by individual patient comorbidities, as objective efficacy of anticholinergic drugs is similar (I-A). Dose escalation does not improve objective parameters and causes more anticholinergic adverse effects. It is, however, associated with improved subjective outcomes (I-A). To decrease side effects, switching to a lower dose or using an extended release formulation or a transdermal delivery mechanism should be considered (I-A).
9. Education on treatment efficacy, realistic expectations, and length of treatment should be offered to patients upon initiation of anticholinergic therapy, as continuation rates for anticholinergic therapy are low (III-B).
10. Oral or transdermal estrogen supplementation should not be recommended for treatment of overactive bladder syndrome as its effects are comparable to placebo (I-E). Vaginal estrogen can be suggested for subjective improvements in overactive bladder syndrome symptoms (III-B).
11. Intravesical botulinum toxin injection and sacral nerve and posterior tibial nerve stimulation are clinically effective options for patients with overactive bladder syndrome unresponsive to conservative options, anticholinergics, or vaginal estrogen (I-A).

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment[a]	Classification of recommendations[b]
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

[a]The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

[b]Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.

Woolf SH, et al. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ 2003;169:207–8.

INTRODUCTION

Overactive bladder syndrome comprises symptoms related to abnormal urinary bladder storage. It is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.[1] It can be associated with detrusor overactivity on urodynamic studies.[1] The prevalence of OAB is reported at 11.8% to 17% in women and significantly increases with age.[2–5] Most women with OAB (96%) report leakage of urine with an overall prevalence of urgency incontinence of 12%.[2] OAB has a greater impact on quality of life than stress urinary incontinence[6,7] and is responsible for several medical comorbidities. Up to 67% of women with OAB report a negative effect on daily living.[4] Significant comorbidities associated with OAB include depression,[8] falls and fractures,[9] and increased admissions to hospitals and nursing homes.[10]

Conservative, pharmacotherapeutic, and surgical interventions are available. This consensus guideline reviews these interventions, focusing mainly on pharmacotherapy.

ABBREVIATIONS

CNS	central nervous system
CYP450	cytochrome p450
ER	extended release
IR	immediate release
OAB	overactive bladder syndrome
XR	extended release

CONSERVATIVE INTERVENTIONS

Conservative management of urinary incontinence has been reviewed in a previous consensus guideline.[11] Many interventions have been described. They include Kegel exercises, functional electrical stimulation, continence pessaries, behavioural management, and bladder training programs.

Recommendation

1. Behavioural management protocols and functional electrical stimulation should be offered in the spectrum of effective primary treatments for overactive bladder syndrome (I-A).

PHARMACOTHERAPEUTIC INTERVENTIONS: ANTICHOLINERGICS

There are currently six approved medications for OAB (Table 2). These are oxybutynin (Ditropan, Ditropan XL, Oxytrol patch, Gelnique gel 10%), tolterodine tartrate (Detrol or Detrol LA), trospium chloride (Trosec IR and XR), solifenacin (VESIcare), darifenacin (Enablex), and fesoterodine (Toviaz).

Mechanism of Action and Drug Properties

Normal human bladder contractions are initiated via muscarinic (cholinergic) receptors in the detrusor muscle.[12] These receptors are of the M2 and M3 subtypes in the bladder.[12] Normal voiding occurs via parasympathetic activation of the M2 or M3 receptors, while the M2 receptors also inhibit sympathetically mediated bladder relaxation.[12,13] Anticholinergic drugs competitively block acetylcholine and increase bladder storage capacity.[14,15]

Table 2. Anticholinergic drugs and properties

Drug	Route		Dose	Receptor selectivity	Main metabolism	CNS penetration
Oxybutynin	Oral	IR	5 mg bid-tid	Non-selective	Hepatic; patch and gel avoid first pass	High
		ER	5 or 10 mg qd			
	Transdermal, patch		3 .9 mg/day; apply twice weekly			
	Transdermal, gel 10%		1 g (1 sachet) qd			
Tolterodine	Oral	IR	2 mg bid	Non-selective	Hepatic	High
		ER (LA)	4 mg qd			
Trospium	Oral	IR	20 mg bid	Non-selective	Renal	Low
			Age > 75:20 mg qd			
		ER (XR)	60 mg qd			
Solifenacin	Oral	5 to 10 mg qd	M3 M1 selective	Hepatic	High	
Darifenacin	Oral		7 .5 to 15 mg qd	M3 selective	Hepatic	Low
Fesoterodine	Oral	ER	4 mg	Non-selective	Hepatic	High
			8 mg			

LA: long acting.

Tolterodine, solifenacin, darifenacin—use ½ dose in hepatic insufficiency; avoid use in severe hepatic insufficiency.

Tolterodine, trospium, solifenacin—use ½ dose when creatinine clearance < 30 mL/min.

All anticholinergics should be prescribed with caution if CYP inhibitors are used concurrently (typical examples are antifungals, antiretrovirals and macrolide antibiotics).

Furthermore, the urothelium also expresses muscarinic receptors and consequently may be the site of action of anti-muscarinics.[16] The release of other substances, such as adenosine triphosphate, may be affected by anticholinergic drugs blocking these urothelial receptors.[17]

Muscarinic receptors are widely distributed throughout the body, and therefore anticholinergic drugs often have undesirable systemic side effects.[14]

Anticholinergics have certain characteristics accounting for slight differences in efficacy and side-effect profiles (Table 3).[18] Most United States Food and Drug Administration- approved agents are tertiary amines with the exception of trospium, a quaternary amine with greater polarity and hydrophilic properties.[18] Smaller molecules, neutral in charge and lipophilic, are more likely to cross the blood–brain barrier and cause central nervous system side effects. These can be immediate (confusion, delirium, headache, blurred vision, dizziness and hallucinations) or delayed (memory loss).[19,20] Specific patient factors such as increased permeability of the blood–brain barrier in older adults, and comorbid diseases predisposing to adverse CNS effects, as well as the intake of other drugs with anticholinergic effects may render individual patients particularly susceptible to antimuscarinic adverse CNS events.[20] Non-selective molecules with some M2 receptor affinity may lead to an increase in heart rate.[19] Some molecules acting on potassium channels within the heart may cause small increases in the QT interval.[19] Tolterodine and solifenacin have led to small increases in the QT interval; on the other hand, darifenacin, fesoterodine, and trospium have not.[19] These small recordable changes in heart function do not seem to cause clinically adverse outcomes.[19] Most anticholinergics are metabolized by the CYP450 system in the liver with the exception of trospium, which undergoes minimal hepatic metabolism. Therefore, other medications or dietary components affecting the CYP450 mechanism may interact with anticholinergic drugs.[19]

Table 3. Published short-term safety of anticholinergics in different populations at time of manuscript preparation

	Elderly and/ or cognitively impaired	Concomitant use of cholinesterase inhibitors	Cardiac	Concomitant use of CYP450 inhibitors
Oxybutynin	–	–	–	–
Tolterodine	✓ IA		✓ IA	
Trospium	✓ IIB	✓ IIB		✓ IIIB
Solifenacin	✓ IB			
Darifenacin	✓ IB		✓ IB	

NOTE: A checkmark indicates "*safe to use*." The corresponding level of evidence is indicated. A dash means the drug is not necessarily unsafe but indicates that safety studies specific to each concern are lacking.

Clinical Efficacy: Anticholinergics Compared With Placebo

A Cochrane Review of 5 of 6 anticholinergic drugs currently on the market concluded that anticholinergics lead to statistically significant improvements in OAB symptoms.[20] The number needed to treat for clinical improvement or cure was 7. On average, patients on anticholinergics had 4 fewer leakage episodes and 5 fewer voids per week when compared with patients on placebo. As anticholinergics are not curative in most instances, clinical success depends on ongoing use; thus a recommendation was made for future trials to include long-term, patient-centred outcomes.

Oxybutynin (Ditropan, Ditropan XL)

Oxybutynin oral preparations have established clinical efficacy when compared with placebo.[20] Oxybutynin IR is also more cost-effective.[21] However, it is associated with significant anticholinergic adverse events in up to 80% of patients[22] and with discontinuation rates of up to 33%.[23] Shortly after treatment initiation, oxybutynin may cause cognitive impairment, and long-term trials of cognitive function while on this anticholinergic are lacking.[24–26]

Two transdermal preparations, a patch (Oxytrol) and a gel (Gelnique 10%), have been developed to improve on the side- effect profile of oral oxybutynin.[27–29] Both preparations have superior clinical efficacy to placebo, with fewer side effects than oral oxybutynin.[27–30] Application site reactions (pruritus and erythema) are more common with the transdermal preparations (14% for the patch and 5% for the gel).[27–29]

Recommendation

2. Oral oxybutynin, immediate and extended release, as well as transdermal oxybutynin, may be offered as treatment for overactive bladder syndrome, as they are associated with significant objective clinical improvement at 12 weeks (I-A). Oxybutynin immediate release has superior cost- effectiveness but more side effects than other anticholinergics (I-A). Adverse events associated with transdermal oxybutynin are fewer than with oral oxybutynin (I-A).

Tolterodine (Detrol, Detrol LA)

Both IR and ER tolterodine are associated with improvements in health-related quality of life and objective OAB parameters in the results of several randomized placebo controlled trials with 12-week duration of follow- up.[30–32] Greater effects are noted in patients with moderate to severe OAB symptoms at baseline.[33] Dry mouth is a common side effect that occurs in one third of patients on tolterodine,[34] but it does not increase the number of treatment discontinuations.[35] Tolterodine does not seem to cause any cardiovascular or CNS adverse effects.[35]

Recommendation

3. Tolterodine, immediate and extended release, may be offered as treatment for overactive bladder syndrome, as it is associated with significant objective clinical improvement at 12 weeks (I-A).

Trospium (Trosec IR and XR)

Trospium, both IR and XR, was associated with improved OAB symptoms in reports from several randomized placebo controlled trials with 12-week duration of follow- up.[20,36,37] Adverse effects are more common than with placebo but do not affect discontinuation rates. The XR formulation significantly improves OAB symptoms and condition-specific quality of life.[38,39]

Trospium has low penetration into the CNS and thus fewer CNS side effects.[36,37,40] In addition, it offers benefits for the bladder and does not affect cognitive function even when used concurrently with a cholinesterase inhibitor for the treatment of Alzheimer's disease.[41] Trospium undergoes minimal hepatic metabolism. Therefore patients who receive concurrent medications that inhibit the CYP450 hepatic metabolism are good candidates for therapy with trospium.[40] Trospium is primarily excreted intact in the urine; however, medications competing for renal elimination, such as digoxin, have not shown significant interactions.[42]

Recommendation

4. Trospium, immediate and extended release, may be offered as treatment for overactive bladder syndrome as it is associated with significant clinical improvement at 12 weeks (I-A). Trospium is an adequate anticholinergic choice for overactive bladder syndrome patients with pre-existing cognitive impairment (II-B) and for overactive bladder syndrome patients taking concurrent CYP450 inhibitors (III-B).

Solifenacin (VESIcare)

Several double-blind placebo-controlled randomized controlled trials with 12-week follow-up support the safety and clinical efficacy of solifenacin compared with placebo.[43–46] Solifenacin also significantly improves the quality of life in patients with OAB symptoms up to 1 year.[46–48] At 1 year, discontinuation rates are low.[46] The incidence of dry mouth in patients on solifenacin is significantly lower than in patients on oxybutynin (35 vs. 83%, $P < 0.001$).[49] The incidence of constipation is 7% to 8%.[43] Solifenacin does not appear

to affect cognitive function, as shown in a pilot randomized trial of healthy elderly volunteers.[50]

Recommendation

5. Solifenacin may be offered as treatment for overactive bladder syndrome, as it is associated with significant objective clinical improvement at 12 weeks (I-A). Solifenacin may be an adequate anticholinergic choice for elderly overactive bladder syndrome patients or patients with pre-existing cognitive dysfunction (I-B).

Darifenacin (Enablex)

The safety and clinical efficacy of darifenacin compared with placebo is shown by three randomized double-blind placebo-controlled multicentre phase III trials with 12-week duration of follow-up.[51–53] The most common side effects are dry mouth and constipation, but discontinuations are rare (0.6% to 2.1% vs. 0.3% in the placebo group).[54] Specifically, women over 65 have a significant improvement in condition-specific quality of life compared with those on placebo.[55]

Because of its M3 receptor selectivity, darifenacin does not affect heart rate.[56] Moreover, darifenacin does not affect memory or other cognitive functions.[57]

Recommendation

6. Darifenacin may be offered as treatment for overactive bladder syndrome, as it is associated with significant objective clinical improvement at 12 weeks (I-A). Darifenacin is an adequate anticholinergic choice for overactive bladder syndrome patients with pre-existing cardiac concerns or cognitive dysfunction (I-B).

Clinical Efficacy: Anticholinergics Compared With Non-Drug Therapies

A Cochrane Review compared the effects of various anticholinergic drugs with those of non-pharmacologic therapies, consisting mainly of bladder training, pelvic floor muscle exercises, and electrostimulation.[58] Thirteen trials, with a total of 1770 participants, were analyzed. Follow-up was up to 24 weeks after initiation of treatment. Tolterodine and oxybutynin had similar cure rates and subjective improvement for OAB when compared with bladder training alone. Objective improvement was better in the anticholinergic group than in the bladder training group. When oxybutynin was compared with a more comprehensive behavioural intervention consisting of pelvic floor muscle exercises, biofeedback, and bladder training, the overall effect subjectively and objectively favoured the behavioural intervention (RR 2.42; 95% CI 1.00 to 5.85).

Oxybutynin or trospium compared with functional electrostimulation yielded no statistically significant difference in cure rates or subjective or objective measures of improvement.[58,59]

Oxybutynin or tolterodine and bladder training compared with bladder training alone showed a subjective advantage of the combination treatment. Tolterodine and bladder training or pelvic floor muscle exercises compared with tolterodine alone did not show any statistically significant difference in subjective improvement.[58]

Since the most recent Cochrane update of this review, an additional randomized controlled trial was published comparing darifenacin with darifenacin and a behavioural modification program consisting of patient education given in a primary physician's office (timed voiding, dietary modifications, Kegel exercises).[60] There were no significant differences between treatment groups in efficacy or health-related quality of life variables.[60]

Recommendation

7. Overactive bladder syndrome patients should be offered a choice between bladder training, functional electric stimulation, and anticholinergic therapy, as there is no difference in cure rates. Combination therapy does not have a clear advantage over one therapy alone (I-A).

Choice of Anticholinergic Drug and Dose

A Cochrane Review analyzed 49 parallel trials comparing different anticholinergics and commonly used doses.[61] Follow-up was mostly 2 weeks to 3 months, except for 2 trials with treatment periods of 1 year or more.

Comparing oxybutynin with tolterodine, there were no differences in subjective or objective cure. There were fewer withdrawals among those taking tolterodine (7% vs. 12%, RR 0.57; 95% CI 0.43 to 0.75), mainly because there were fewer side effects.[61] There were no statistically significant differences in outcomes when oxybutynin and trospium were compared. When several doses of tolterodine were studied, ranging from 0.5 mg twice daily to 4 mg twice daily, there were no statistically significant differences in objective improvement or withdrawals because of side effects. Subjective cure was more likely with the higher doses, but these higher doses were more commonly associated with high post-void residuals and dry mouth. Subjective cure was also more likely with higher doses of extended release oxybutynin (10 mg vs. 5 mg daily). Oxybutynin, 2.5 mg 3 times daily and 2.5 mg used as needed were equally effective in terms of objective measures of improvement. Trospium 40 mg daily and twice daily dosing had similar effects in terms of objective

measures of improvement. Extended release preparations of both oxybutynin and tolterodine, including the extended release oxybutynin patch, were associated with less dry mouth than immediate release preparations.[61]

Several other comparative randomized controlled trials comparing anticholinergics have been published since the most recent Cochrane Review update. One trial compared solifenacin 5 mg and 10 mg daily with tolterodine extended release 4 mg daily.[62] Subjective cure was significantly more common in the solifenacin group (59% vs. 49%, $P = 0.006$). Objective measures of improvement and withdrawals because of side effects were not significantly different between the groups. Another trial comparing darifenacin 15 mg and 30 mg daily with oxybutynin 5 mg 3 times daily showed comparable efficacy and improved tolerability of darifenacin.[63] The other trials compared fesoterodine 4 mg and 8 mg daily with tolterodine extended release 4 mg daily.[64,65] Fesoterodine was superior to tolterodine on several objective measures of improvement such as urge incontinence episodes, severe urgency with incontinence, mean voided volume, and number of continent days per week. Diary dry rates were significantly better in the fesoterodine group than in the tolterodine group (64% vs. 57%; $P = 0.015$).[64,65]

Recommendation

8. The choice of anticholinergic therapy should be guided by individual patient comorbidities, as objective efficacy of anticholinergic drugs is similar (I-A). Dose escalation does not improve objective parameters and causes more anticholinergic adverse effects. It is, however, associated with improved subjective outcomes (I-A). To decrease side effects, switching to a lower dose or using an extended release formulation or a transdermal delivery mechanism should be considered (I-A).

Contraindications

Absolute contraindications to anticholinergic use include urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and known hypersensitivity to the individual drugs or any of their ingredients.

Relative contraindications that warrant cautious use include partial bladder outlet obstruction (borderline or high post-void residuals), controlled narrow-angle glaucoma, impaired cognitive function, reduced renal or hepatic function, concomitant excessive alcohol use (added sedating effects), decreased gastrointestinal motility, constipation, and myasthenia gravis. Elderly patients in particular should be monitored for drug interactions or polypharmacy of drugs with anticholinergic effect (e.g., antidepressants, antipsychotics, anxiolytics), as the overall anticholinergic load is associated with confusion, falls, and fractures.[66] Anticholinergics are category C drugs in pregnancy, to be used only if the benefits clearly outweigh the risk.

Adherence and Continuation Rates

Patient adherence to a prescribed anticholinergic treatment plan has been shown to be low. In a study of oxybutynin and tolterodine ER and IR prescriptions in 1117 adult patients, only 13.2% persisted with treatment for at least 1 year, with a median time to discontinuation of 31 days.[67] Adherence was significantly better but still suboptimal for the extended release formulations.[67] In another trial of patients on immediate release oxybutynin, at 2-year follow-up, 67% of respondents had stopped drug therapy, most within 2 months of initiation.[68] Reasons for discontinuation were adverse effects (24%) and symptomatic improvement or cure (53%).[68] White ethnicity, previous hospitalization length, starting with tolterodine or oxybutynin extended- release, and previous use of topical drugs or antipsychotics were associated with increased adherence to anticholinergics during a 6-month period.[69] Previous depression or urinary tract infection diagnosis and polypharmacy significantly increased the odds of early discontinuation.[69] Patient counselling about efficacy of treatment, realistic expectations, and length of treatment was recommended to improve long-term adherence to anticholinergic therapy.[70]

Recommendation

9. Education on treatment efficacy, realistic expectations, and length of treatment should be offered to patients upon initiation of anticholinergic therapy, as continuation rates for anticholinergic therapy are low (III-B).

PHARMACOTHERAPEUTIC INTERVENTIONS: ESTROGENS

The lower urinary tract (urethra and trigone) derives from the cloaca, which shares an embryological origin with the lower vaginal canal. Therefore, the trigonal squamous epithelium differs from the transitional epithelium and undergoes squamous metaplasia. The urethral mucosa is continuous with the squamous epithelium of the vestibule. Both areas are hormonally sensitive.[71] A Cochrane Review examined the effect of estrogen supplementation on urinary incontinence in postmenopausal women.[72] Heterogeneous evidence derived from trials investigating other conditions such as stress urinary incontinence and using greater than low dose vaginal estrogen of different types, showed that

there were 1 to 2 fewer voids in 24 hours and nocturnal voids amongst women treated with local estrogen.[72] A small trial showed modest benefit from vaginal estriol ovules in prevention of symptoms of urgency and frequency after tension-free vaginal tape placement.[72]

Oral estriol or a subcutaneous estradiol implant were not significantly better than placebo for OAB symptoms.[73,74]

Recommendation

10. Oral or transdermal estrogen supplementation should not be recommended for treatment of overactive bladder syndrome as its effects are comparable to placebo (I-E). Vaginal estrogen can be suggested for subjective improvements in overactive bladder syndrome symptoms (III-B).

PHARMACOTHERAPEUTIC INTERVENTIONS: OTHER DRUG OPTIONS

There is a long list of medications with anticholinergic effects, few of which have been studied as treatment specifically for overactive bladder. Tricyclic antidepressants such as imipramine and amitryptyline have been used for overactive bladder. With a dual activity as an anticholinergic (to relax the detrusor) and an alpha agonist (to contract the urethral sphincter), they have adequate biologic plausibility for the treatment of urinary urge incontinence. Unfortunately, their anticholinergic activity is weaker than that of modern bladder anticholinergics.[75] There is minimal evidence to support the use of imipramine for urinary incontinence in the elderly.[75] There are no randomized controlled trials to compare tricyclics with modern anticholinergics used to treat overactive bladder.[75]

REFRACTORY OAB

Options for OAB symptoms resistant to anticholinergic therapy are limited and costly. These options include but are not limited to local bladder therapies such as botulinum toxin type A detrusor injections, central neurostimulation, and peripheral neurostimulation (e.g., tibial nerve).

Botulinum toxin for OAB (100 to 300 units injected into the detrusor muscle) has been shown, in several randomized controlled trials, to reduce number of voids and urgency and incontinence episodes per day and to improve maximum cystometric capacity and condition-specific quality of life.[76] Generally, around 80% of patients treated with botulinum toxin experienced improvement, with some patients requiring reinjection for recurrence of OAB symptoms.[76] Overall patient satisfaction with botulinum toxin was high.[76] The most common complication related to intravesical botulinum toxin was transient urinary retention. Up to 43% of patients needed clean intermittent self-catheterization, and the incidence of retention was reported to be dose-dependent.[76]

There are also data from randomized controlled trials to support the use of sacral nerve stimulation. Good clinical response, with improvement on several objective measures of OAB severity, was reported in 64% 88% of patients, and clinical success seems to persist in the long term. Subjective outcomes are also favourable.[76] However, lead migration, pain, and infection result in a 33% reoperation rate to treat these complications.[77]

Another form of neurostimulation, tibial nerve stimulation, is gaining acceptance. Two double-blind randomized sham-controlled trials showed significant objective and subjective improvements in OAB when compared with placebo.[78,79] Treatment benefit was sustained at 12 months.[80] A randomized controlled trial of tibial nerve stimulation versus tolterodine showed similar objective improvement and superior subjective improvement or cure at 12 weeks.[81]

Recommendation

11. Intravesical botulinum toxin injection and sacral nerve and posterior tibial nerve stimulation are clinically effective options for patients with overactive bladder syndrome unresponsive to conservative options, anticholinergics, or vaginal estrogen (I-A).

CONCLUSION

Overactive bladder syndrome is a common bothersome condition. Options for therapy include behavioural, pharmacologic, and surgical interventions. Pharmacotherapy for OAB includes anticholinergics and local vaginal estrogen. Anticholinergics have been shown to offer some symptomatic improvement over placebo, with a strong placebo therapeutic effect noted. Anticholinergics are similar to behavioural therapy and electrical stimulation in clinical efficacy. They have significant side effects that need to be carefully considered along with individual patient comorbidities. Newer formulations, particularly those administered transdermally, have been shown to have a better side-effect profile. Long-term effects of anticholinergics and patient- centred outcomes should be the focus of future studies.

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