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No. 353-Treatments for Overactive Bladder: Focus on Pharmacotherapy – An Addendum

This Technical Update Addendum has been prepared by the Urogynaecology Committee, reviewed by the Guideline Management and Oversight Committee and approved by the Board of the SOGC.

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Key Words: Overactive bladder, urgency, frequency, urinary incontinence, fesoterodine, anticholinergic, mirabegron, β3 agonist

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Abstract

Objective: This technical update addendum reviews success rates and comparative evidence of the anticholinergic fesoterodine, as well as mechanism of action, safety profile, success rates, and comparative evidence of the β3 agonist mirabegron in the treatment of non-neurogenic overactive bladder syndrome (OAB). This adds to OAB pharmacotherapy recommendations initially published in 2012.

Intended Users: Residents and other trainees, primary care practitioners, gynaecologists, urologists, urogynaecologists, and other health care providers who assess, counsel, and treat women with OAB.

Target Population: Adult women with symptomatic OAB.

Options: This addition relates to fesoterodine, mirabegron, and anticholinergic-β3 agonist combination pharmacotherapy.

Outcomes: The outcomes of interest are clinical efficacy of fesoterodine compared with no treatment or other OAB therapies; mechanism of action and safety profile of mirabegron, clinical efficacy of mirabegron compared to no treatment or other OAB therapies; clinical efficacy of anticholinergic-β3 agonist combination pharmacotherapy for OAB.

Evidence: PubMed, Medline, and the Cochrane Database were searched using the key words “fesoterodine” and “mirabegron.” Results were restricted to English or French and human clinical and pharmacological research. Animal research and clinical studies including only male participants were excluded. Articles were included until the end of December 2016. Grey literature was not searched. Clinical practice guidelines, guidelines of specialty societies, and systematic reviews were included. RCTs and observational studies were included when evidence for the outcome of interest or in the target population was not available from systematic reviews. New studies not yet included in systematic reviews were also included. References of included articles were also searched to ensure comprehensive inclusion of relevant literature.

Values: The content and recommendations were drafted and agreed upon by the principal author, as well as members of the Urogynaecology Committee. The Board of the SOGC approved the final draft for publication. The quality of evidence was rated using the criteria described in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology framework. The Summary of Findings is available upon request.

Benefits, Harms, and/or Costs: It is expected that this technical update will benefit patients with OAB by providing physicians and other interested health care providers with additional options for and knowledge of safe and effective OAB pharmacotherapy. The benefits clearly outweigh the potential harms or costs of implementation of this technical update, although there are no direct harms or costs identified.

Updates: "Evidence will be reviewed 5 years after publication to decide whether all or part of the document should be updated. However, if important new evidence is published prior to the 5-year cycle, the review process may be accelerated for a more rapid update of some recommendations."

Sponsors: Not applicable.

Recommendations:

1. Fesoterodine is recommended as a treatment for overactive bladder (Strong, High).
2. Dose escalation of fesoterodine is recommended for improved clinical efficacy, as it is associated with significant subjective and objective clinical improvement, both short and long term (Strong, High).
3. Fesoterodine is recommended as an anticholinergic of choice for overactive bladder symptoms in elderly and frail elderly (Strong, High).
4. Fesoterodine is recommended for overactive bladder symptoms in patients with pre-existing cardiac concerns or cognitive dysfunction (Strong, Moderate).
5. Fesoterodine is recommended for nocturnal overactive bladder symptoms to improve sleep quality (Conditional, High).
6. Mirabegron is recommended as a treatment for overactive bladder (Conditional, High).
7. Mirabegron is recommended for overactive bladder symptoms in patients with intolerable side effects or suboptimal response on anticholinergic therapy (Strong, Moderate).
8. Mirabegron may be used in combination with solifenacin 5 mg for overactive bladder symptoms as an alternative to solifenacin 10 mg to decrease anticholinergic side effects of the higher dose solifenacin (Conditional, High).

INTRODUCTION

OAB encompasses bladder storage symptoms of increased urinary urgency, frequency, and nocturia with or without urgency urinary incontinence in the absence of urinary tract infection or other pathology (including neurological).[1] This technical update is an addition to the previously published, and still valid, technical update, *Treatments for Overactive Bladder: Focus on Pharmacotherapy* (2012); clinicians should consult both documents for various treatment options when choosing the most appropriate pharmacotherapeutic agent for OAB (Table 1). The current update covers recently introduced therapies using an anticholinergic drug (fesoterodine), a β3 agonist (mirabegron), and combination therapies of anticholinergics and mirabegron.

BODY OF TECHNICAL UPDATE/SECTIONS

Fesoterodine

Fesoterodine was approved by Health Canada as an antimuscarinic for treatment of overactive bladder in 2012. It is a non-specific competitive muscarinic receptor antagonist available in 4-and 8-mg doses.[4] It is first rapidly and extensively hydrolyzed into the active metabolite, 5-hydroxymethyl tolterodine by non-specific esterases in the gut and then further CYP2D6- and CYP3A4-metabolized in the liver.[5] Its main metabolite is transported out of the CNS via an active P-glycoprotein efflux transporter, and thus has low CNS penetration.[6]

Fesoterodine Contraindications

Contraindications and precautions are identical to older anticholinergics.[7] Fesoterodine is contraindicated in gastric or urinary retention, uncontrolled narrow angle glaucoma, and severe myasthenia gravis. It should not be administered in severe hepatic impairment. Patients with severe renal impairment (creatinine clearance <30 mL/min) or concomitant use of CYP inhibitor medications should not receive more than 4 mg daily.[7] It does not prolong QT interval.[5]

Fesoterodine Clinical Efficacy

Several double-blind, prospective, RCTs with 12-week follow-up have demonstrated the safety and clinical efficacy of fesoterodine for OAB symptoms of frequency, urgency, and incontinence at both 4- and 8-mg doses compared with placebo.[8–10] Dose escalation from 4 to 8 mg was shown to improve clinical efficacy.[11] Improvements were not affected by age.[12] Longer-term treatment was shown to be well-tolerated and associated with sustained clinical efficacy for ≥24 months[13–15] and in patients ≥65[16] specifically. The safety and clinical efficacy of fesoterodine administration in the elderly and frail elderly have been studied more than for any other available OAB anticholinergic to date.[17] The FORTA classification was introduced to guide clinicians with various drug choices in the elderly. Drugs are qualified as Class A (absolutely), Class B (beneficial), Class C (careful), and Class D (don't use).[18] Fesoterodine was classified as FORTA Class B (beneficial). In contrast, all other OAB anticholinergics were ranked Class C.[18] In the elderly, fesoterodine was associated with more dry mouth (34%) and constipation (9%) than placebo.[17,19] Incidence of urinary retention in vulnerable elderly was similar to placebo.[17] Cardiovascular and CNS-related adverse events were rare; cognition was not affected over 12 weeks of treatment.[17,19,20] Subjective and objective outcomes, including caregiver impact outcomes, were significantly improved compared to placebo.[17] Overall, discontinuation rates were similar to placebo.[17] Outside of large clinical trials, in routine clinical practice—although long-term continuation of use was low over 52 weeks or more with all studied anticholinergics—they were significantly higher for fesoterodine (35.8% continuation vs. 31.9% solifenacin and 30.9% tolterodine).[21]

Fesoterodine 8 mg was shown to significantly reduce the number of nocturnal micturitions compared to placebo,[22–24] decrease nocturnal urgency episodes,[23] and improve subjective sleep quality on validated sleep/energy questionnaires.[24] This was not shown or inconsistently reported in earlier trials comparing other anticholinergics to placebo.[8,9,25]

A Cochrane systematic review of 3 RCTs comparing fesoterodine 8 mg with tolterodine ER 4 mg showed statistically significantly better condition-specific quality of life and patient-reported cure favouring fesoterodine (74% cured vs. 66% for tolterodine).[26] Meta-analysis showed significantly lower number of micturitions, leakage episodes, and urgency per 24 hours favouring fesoterodine 8 mg. However, withdrawals due to adverse events and dry mouth were higher in the fesoterodine 8 mg versus tolterodine ER 4 mg.[26] There was no difference in efficacy or dry mouth when fesoterodine 4 mg was compared with tolterodine ER 4 mg.[26] Patients receiving fesoterodine 4 mg were between 34% and 58% less likely to experience dry mouth compared to 8 mg.[26] Dry mouth at 29% was by far the most common side effect of

ABBREVIATIONS

CNS	central nervous system
FORTA	Fit fOR The Aged
OAB	overactive bladder syndrome
RCT	randomized control trial

Table 1. Key to grading of recommendations, assessment, development and evaluation (GRADE)[2,3]

Strength of the recommendation	Definition
Strong	Highly confident of the balance between desirable and undesirable consequences (i.e., desirable consequences outweigh the undesirable consequences; or undesirable consequences outweigh the desirable consequences).
Conditional (weak)[a]	Less confident of the balance between desirable and undesirable consequences.
Quality level of a body of evidence	**Definition**
High|++++	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate|+++0	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low|++00	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low|+000	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

[a]Conditional recommendations should not be misinterpreted as weak evidence or uncertainty of the recommendation.

Examples:

Strong, Moderate|+++0: Strong Recommendation, Moderate Quality of Evidence.

Conditional, Low|++00: Conditional.

Recommendation, Low Quality of Evidence.

fesoterodine 8 mg (15% ER tolterodine, 6% placebo); the second most common was constipation at 5% (4% ER tolterodine, 2% placebo).[22] Most other treatment-related side effects were rare and minor.[22]

In patients who had a suboptimal response to tolterodine ER 4 mg, fesoterodine 8 mg performed significantly better than placebo in subjective and objective outcomes.[27]

To date, the clinical efficacy of fesoterodine has not been compared in RCTs as monotherapy or combination therapy, to non-drug conservative therapies such as bladder training, to anticholinergics other than tolterodine, to the β3 agonist mirabegron, or to refractory OAB therapy such as botulinum toxin or neurostimulation. Because it is more efficacious than tolterodine, it may also perform better when compared to conservative therapies, but this needs to be further explored.[28]

Recommendations

1. Fesoterodine is recommended as a treatment for overactive bladder (Strong, High).
2. Dose escalation of fesoterodine is recommended for improved clinical efficacy, as it is associated with significant subjective and objective clinical improvement, both short and long term (Strong, High).
3. Fesoterodine is recommended as an anticholinergic of choice for overactive bladder symptoms in elderly and frail elderly (Strong, High).
4. Fesoterodine is recommended for overactive bladder symptoms in patients with pre-existing cardiac concerns or cognitive dysfunction (Strong, Moderate).
5. Fesoterodine is recommended for nocturnal overactive bladder symptoms to improve sleep quality (Conditional, High).

Table 2. Judgement and interpretation of strong and conditional recommendations[2,3]

Judgement/Interpretation	Strong recommendation, "We recommend…"	Conditional (weak) recommendation, "We suggest…"
Judgement by guideline panel	It is clear to the panel that the net desirable consequences of a strategy outweighed the consequences of the alternative strategy.	It is less clear to the panel whether the net desirable consequences of a strategy outweighed the alternative strategy.
Implications for patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Implications for clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual to arrive at a management decision consistent with his or her values and preferences.
Implications for policy makers	The recommendation can be adopted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders

MIRABEGRON

For many decades, anticholinergic drugs have dominated the pharmacotherapy landscape of OAB. Given their incomplete clinical efficacy, bothersome side effect profile, and poor long-term continuation rate, research has emerged on a new class of drugs, the β3 agonists. Mirabegron is the first drug in this class to be approved for OAB treatment. Health Canada approved it for this indication in 2013. Mirabegron is also approved in Japan, Europe, and the United States. In the United States and Canada, doses of 25 and 50 mg are available with dose escalation to improve therapeutic benefit. In Japan and Europe, 50 mg are usually used, with dose reduction in cases of severe renal and moderate hepatic impairment.[29]

Mirabegron Mechanism of Action

Afferent Aδ fibres in the detrusor muscle and C fibres in the urothelium and lamina propria of the bladder carry sensations of fullness to the human brain. Subsequently, if voiding can occur, efferent parasympathetic fibres release acetylcholine, causing detrusor contraction and emptying of the bladder. Alternatively, if voiding needs to be delayed, efferent sympathetic fibres release adrenaline, causing detrusor relaxation to improve urine storage. Adrenergic receptors exist in 3 varieties throughout the body: β1, β2, and β3. The β3 subtype constitutes 95% of adrenoreceptors found in the human bladder. Mirabegron is a selective β3 adrenoceptor agonist. It improves urine storage by stimulating sympathetic detrusor and urothelium receptors.[30] It also decreases Aδ and C fibre afferent activity,[31] thus decreasing spontaneous bladder contractions and the sensation of urgency in response to bladder filling. Mirabegron has α-adrenoceptor antagonist activity in animal studies;[32] although this action could theoretically cause urethral relaxation in humans, there seems to be no clinical evidence of such an effect.[31]

Mirabegron Pharmacology

Following oral administration, mirabegron is rapidly absorbed and metabolized in the liver.[29,33,34] It is excreted mainly in the unchanged form in urine and feces.[33] Drugs metabolized via the human CYP enzymes may have interactions with mirabegron. Additionally, dose adjustments need to be made in patients with severe renal impairment and moderate or severe hepatic impairment.[35] Body weight or timing and composition of meals do not warrant mirabegron dose adjustments.[36–38] Pharmacokinetic interactions between mirabegron and several drugs have been studied. The only studied drug which may require dose adjustments and close monitoring of levels is digoxin.[29,39–42]

Mirabegron Safety and Side Effects

Phase I studies showed mirabegron to be generally well-tolerated at doses up to 300 mg in men and women under age 65, and up to 200 mg in men and women 65 and older.[43]

Overall, mirabegron had a low incidence of CNS effects such as headache or dizziness (similar to placebo), but long-term data and studies on OAB patients with dementia or other neurological diseases are currently lacking.[30,44,45]

Mirabegron at a supratherapeutic dose of 100 mg did not increase the intraocular pressure of healthy adult volunteers over 8 weeks of treatment, suggesting possible safety in the context of glaucoma.[46]

Mirabegron has been extensively studied for cardiovascular safety. A phase II dose-ranging study in OAB patients and up to 200 mg mirabegron showed a small statistically significant increase in pulse rate, with no increased incidence of cardiovascular adverse events.[47] At the supratherapeutic dose of 200 mg—in female participants only—mirabegron was also shown to prolong the QT interval, suggesting a pro-arrhythmic effect.[48] A systematic review of clinical studies of cardiovascular safety showed mirabegron to be comparable, at current therapeutic doses, to commonly used anticholinergic medication and placebo.[42,49] Although mirabegron did show a slight increase in blood pressure (5 mmHg for systolic BP) of healthy adult volunteers, this increase was not significant versus placebo in the OAB population with typical cardiovascular comorbidities such as controlled hypertension or diabetes.[42] A low proportion of OAB patients (5%) on mirabegron 25- and 50-mg doses experienced tachycardia adverse events. Serious cardiovascular adverse events did not occur[50] or were similar to placebo.[42] However, caution must be exercised in patients with poorly controlled cardiovascular risk factors such as hypertension, arrhythmia, angina, heart failure, or in patients over 80 years old. In these cases, risk factors should be controlled prior to initiation of therapy and/or periodic blood pressure and heart rate monitoring should be maintained.[42,51]

Side effects of dry mouth and constipation typical with anticholinergics and responsible for treatment discontinuation were not found to be associated with mirabegron use, as their frequency was similar to placebo during mirabegron therapy.[30] A randomized trial of mirabegron 50 and 100 mg versus tolterodine ER 4 mg over 12 months of follow-up showed side effects to be similar between groups, with the exception of dry mouth, which was more than three-fold higher in the tolterodine group.[52]

Incidence of urinary retention remained similar to placebo at various mirabegron doses[47] and was very low over 12

months of mirabegron therapy;[52] however, studies to date have only included women with normal baseline post-void residual measurements.

Several studies have shown mirabegron continuation rates to range from 12.2% to 39% at 12 months.[53–55] The main reason for mirabegron discontinuation was lack of clinical efficacy in all studies.[53,54,56] Treatment-naïve patients were more likely to discontinue mirabegron than those who had previously taken anticholinergics.[54,55] A large Canadian retrospective study of 19 485 patients—in majority female and treatment-naïve—showed significantly greater adherence to mirabegron compared with anticholinergics (32% vs. 14%–22% respectively).[55]

Because pharmacological OAB treatments are common in patients >65, it is important to evaluate their safety in the elderly and frail elderly. Mirabegron is currently classified as FORTA Class C (potentially harmful if not properly monitored); however, this may change with further long-term safety data.[18] A pooled analysis of three mirabegron randomized trials for a subgroup of patients ≥65 and ≥75 showed mirabegron may be safer and better tolerated compared with anticholinergics.[44]

Mirabegron Clinical Efficacy

After initial dose-ranging studies,[47,57] the clinical efficacy of mirabegron was investigated in several phase III prospective randomized double-blind trials. Comparisons were to placebo[58–60] and/or tolterodine ER 4 mg daily.[52,60,61] A systematic review and meta-analysis of six mirabegron RCTs concluded that mirabegron was more effective overall than placebo at treating OAB symptoms such as frequency and incontinence.[62] Compared to placebo, mirabegron was associated with a lower number of incontinence episodes per 24 hours (mean difference −0.54; 95% CI −0.63 to −0.45; $P = 0.001$) and a lower number of micturitions per 24 hours (mean difference −0.55; 95% CI −0.63 to −0.47; $P = 0.001$).[62] Mirabegron was more effective than tolterodine at decreasing the number of daily incontinence episodes per 24 hours (mean difference −0.25; 95% CI −0.43 to −0.06; $P = 0.009$) with a similar number of micturitions per 24 hours and while maintaining a lower adverse reaction rate.[62] Similar to anticholinergic trials, placebo effect is extremely strong in mirabegron trials. An example is a more recent randomized trial of mirabegron 50 mg versus tolterodine ER 4 mg versus placebo performed in a slightly younger population with less severe baseline incontinence.[63] This trial barely demonstrated statistical significance of mirabegron versus placebo, with 0.57 fewer micturitions per 24 hours. Tolterodine effect was not significantly better than placebo.[63] A post hoc analysis of pooled data from 3 RCTs demonstrated that mirabegron treatment efficacy for incontinence and urgency episodes increased with increasing severity of incontinence at baseline.[64]

A randomized trial of mirabegron 50 and 100 mg versus tolterodine ER 4 mg examined outcomes at 12 months.[52] Similar to tolterodine, sustained clinical efficacy was observed for mirabegron (both doses), with decreased number of voids and incontinence episodes over 24 hours, improvements in voided volume, nocturia, condition-specific quality of life, and satisfaction scores.[52] Cure of incontinence was noted in 43.4% and 45.1% of mirabegron 50 mg and tolterodine ER 4 mg groups respectively.[52]

The concept of using mirabegron as a second-line therapy in patients dissatisfied with one or more prior anticholinergic OAB drugs because of lack of clinical efficacy has been investigated in a large randomized non-inferiority trial of mirabegron 50 mg versus solifenacin 5 mg for 12 weeks.[65] Clinically relevant and similar improvement in OAB parameters was noted with both therapies.[65] Subjectively, 60% of patients reported improvement in OAB symptoms and related quality of life after failing to improve with at least one anticholinergic medication.[66] A post hoc analysis of a phase III randomized trial showed numerical improvements in micturition and incontinence frequency with mirabegron in patients who had had poor tolerability on anticholinergic therapy; however, further prospective trials need to be undertaken to confirm these results.[67]

Outside of clinical trials and using subjective patient outcomes only, mirabegron showed modest clinical benefits, with 11% of patients describing themselves as "very much better" and 23% "much better."[68]

To date, the clinical efficacy of mirabegron has not been compared in RCTs as monotherapy or combination therapy, to non-drug conservative therapies such as bladder training, to many newer anticholinergics such as fesoterodine, or to refractory OAB therapy such as botulinum toxin or neurostimulation.

Recommendations

6. Mirabegron is recommended as a treatment for overactive bladder (Conditional, High).
7. Mirabegron is recommended for overactive bladder symptoms in patients with intolerable side effects or suboptimal response on anticholinergic therapy (Strong, Moderate).

COMBINATION THERAPY

Combining a β3 agonist with an anticholinergic has theoretical advantages of a synergistic effect. To date, the only

anticholinergic studied in combination with mirabegron has been solifenacin. A phase II dose exploration trial investigated solifenacin plus mirabegron versus solifenacin or mirabegron monotherapy at various doses (solifenacin up to 10 mg and mirabegron 25 or 50 mg).[69] Combination therapy significantly improved 24-hour symptoms when compared to solifenacin 5 mg monotherapy: mean voided volume (adjusted difference range 18 mL to 26.3 mL), micturition frequency (−0.8 to −0.98), and urgency episodes (−0.98 to −1.37). Incontinence episodes were not significantly improved by combination therapy with mirabegron 50 mg compared with placebo or solifenacin 5 mg alone. OAB improvements were generally not significant with combination therapy when compared with solifenacin 10 mg alone.[69] With the exception of constipation, adverse events were not increased with combination therapy.[69] Another trial investigated the addition of mirabegron 25 or 50 mg in non-responders to solifenacin 2.5 or 5 mg.[70] Add-on therapy was well-tolerated and associated with significant improvement in condition-specific quality of life, number of micturitions/24 hours, urgency, nocturia, and urge incontinence episodes/24 hours.[70] A similar trial design used a solifenacin dose of up to 10 mg to show combination therapy was non-inferior to solifenacin 10 mg for key secondary endpoints and superior for improving daily micturitions.[71] Overall, combination trials seem to suggest some benefit compared with anticholinergic monotherapy at the lower dose, but this benefit seems similar to that achieved by anticholinergic monotherapy dose escalation with fewer side effects. The cost of combination therapy may be prohibitive. Therapeutic combinations with various other anticholinergics need to be investigated in further trials.

Recommendation

8. Mirabegron may be used in combination with solifenacin 5 mg for overactive bladder symptoms as an alternative to solifenacin 10 mg to decrease anticholinergic side effects of the higher dose solifenacin (Conditional, High).

CONCLUSION

Fesoterodine is the newest addition to the list of anticholinergics for OAB. It is well-studied in the elderly and has no cardiovascular or neurological side effects. It shows promise in the treatment of nocturnal OAB symptoms and for OAB refractory to tolterodine therapy. Mirabegron is the first β3 adrenoceptor agonist for OAB on the Canadian market. Further research is needed before mirabegron can be widely accepted as first-line OAB drug therapy; until then, mirabegron has a role in the treatment of patients who experience intolerable side effects from anticholinergic therapy or as an alternative when clinical response to anticholinergics is suboptimal. Combination therapy between anticholinergics and mirabegron has been minimally studied and cannot be strongly recommended at this time.

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