

NON-SYSTEMATIC REVIEW

UROLOGY

Which drugs are best for overactive bladder? From patients' expectations to physicians' decisions

Ian Milsom¹  | Adrian Wagg² | Matthias Oelke³ | Christopher Chapple⁴

¹Department of Obstetrics and Gynecology, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden

²Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

³Department of Urology, Pediatric Urology and Urologic Oncology, St. Antonius Hospital, Gronau, Germany

⁴Department of Urology, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Sheffield, United Kingdom

Correspondence

Ian Milsom, Department of Obstetrics and Gynecology, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden.

Email: ian.milsom@gu.se

Abstract

Aim: In order to help physicians determine which drugs are the best for treating overactive bladder (OAB) symptoms, this review considered three questions: what are the patient's expectations? What information is generated by the Multicriteria Decision Analysis (MCDA) model? What can physicians expect from medical treatments?

Methods: A comprehensive literature search was undertaken on these three topics in order to assist physicians regarding the optimum treatment modality for OAB.

Results: Patients' difficulties in reporting symptoms and their expectations of treatment outcomes interfere with the success of treatment. To assist physicians in meeting patients' expectations and to choose the most appropriate treatment, a new approach, recognised by the European Medicines Agency, the MCDA model was used to compare the benefits and safety of OAB treatments.

Conclusion: The MCDA model is useful for comparing the benefit-safety profiles of OAB drugs in order to equip clinicians with information on the drug that might best meet their patient's needs. Flexibly dosed fesoterodine appeared to be most efficacious in resolving urgency and urgency incontinence compared with other drugs, and resolution of urinary urgency appears to be associated with a reduced number of reported adverse events.

1 | INTRODUCTION

The often-quoted statement that the bladder is an unreliable witness¹ refers to the fact that lower urinary tract symptoms (LUTS) are nonspecific and may be caused by different pathologies. The clinical diagnosis of overactive bladder (OAB) requires urinary urgency to be present.² Patients may report their symptoms differently and clinicians must interpret what patients tell them. For example, OAB presents differently in men and women.³ OAB-dry is more common in men, whereas OAB-wet is more common in women. Older men are particularly concerned about benign prostatic enlargement as the cause of their LUTS.⁴

For many patients, OAB treatment includes pharmacotherapy. All OAB drugs have been tested against placebo; however, there is limited information on the comparative efficacy and tolerability of these drugs; notably, from head-to-head comparisons. The European

Association of Urology (EAU) guidelines on urinary incontinence attempt to rank OAB drugs by calculating the number needed to treat in order to give some perspective on their relative efficacy.⁵ However, recently, the European Medicines Agency (EMA) has recommended the use of a Multicriteria Decision Analysis (MCDA) model to compare data from randomised clinical trials (RCTs).⁶

2 | METHODS

This review is based on a comprehensive literature search undertaken to assist physicians to determine which drugs are the best for treating OAB symptoms. The review considered three questions: What are the patient's expectations? What information is generated by a MCDA model? What can physicians expect from medical treatments? These

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topics were debated during the symposium entitled “Which Drugs Are Best for OAB? From Patients’ Expectations to Physicians’ Decisions”, which took place at the 34th Annual Congress of the EAU in March 2019 in Barcelona, Spain.

2.1 | Expectations and concerns in overactive bladder: Patient perspectives

The major driver of OAB, and therefore an essential component of the definition of OAB,⁷ is urinary urgency. This leads to increased diurnal and nocturnal micturition frequency, decreases the interval between voids, and at its extreme, urgency urinary incontinence (UUI).^{2,8} A survey of 1916 men and women with OAB in six European countries found that 40% of participants had never spoken to a physician; 32% had discussed their symptoms but had never tried a drug; 28% had received a drug, while among these patients, only 57% were currently receiving pharmacotherapy.⁹ Thus, the following questions should be asked: why do some patients remain silent about their complaint? What words do patients use to report their symptoms when they do so?

Urgency is defined by the International Continence Society as “a sudden compelling desire to pass urine which is difficult to defer”.^{7,10,11} In its extreme form, urgency cannot be suppressed; the desire to void cannot be stopped and the patient may experience incontinence if he/she does not reach the toilet quickly enough. Urgency is not life-threatening but has a significant impact upon quality of life; the amount of bother increases and overall quality of life decreases as the number of urgency episodes increases.¹² Some patients do not mention urgency; they are either embarrassed or think it is not serious because “it is not cancer”, or that it is normal for getting older. People also deny their incontinence.¹³ The words used by patients to express urgency have been investigated in a qualitative study¹⁴; they include: “urgent; necessary; right now; too often; when I have to go, I have to go; it comes suddenly; piercing; first wave is ‘bam’ with no warning...”.

Physicians need to consider the patient's symptoms and their treatment expectations and moderate these in the light of the available evidence regarding the effectiveness of treatments. For example, when experiencing 20 voids and five UUI episodes per day, a patient may expect to be dry all the time with no side effects; but the physician should explain that, at best, the reduction in number of UUI episodes will reach 70%, the number of voids may decrease by 20% and treatment-associated side effects may occur (Table 1).¹⁵

When expectations are unrealistic or at variance, the treatment plan may not be simple and may contribute to poor adherence.^{15,16} Moreover,

Review criteria

- A comprehensive literature search was undertaken on:
- Patient's expectations of OAB/urinary incontinence management
- Multicriteria Decision Analysis (MCDA) models
- Physicians expectations from medical treatment of OAB and urgency incontinence

Message for the clinic

- Patients are often reluctant to report their problems and may have unrealistic expectations of treatment
- Physician support is an important aspect of treatment, and good communication skills will improve adherence to OAB treatment
- MCDA modelling provides valuable information by comparing the benefit-safety profiles of OAB drugs
- Fesoterodine is an effective drug and when compared with other medications, flexibly dosed fesoterodine has the most favourable benefit-safety profile

the therapeutic relationship with the clinician will influence treatment. Studies have shown that patients seeking medical treatment for OAB often report negative experiences of their encounters with healthcare providers.¹⁷ Some physicians may also consider that urgency/UUI is normal with ageing, or that it is because of a urinary tract infection (UTI). In a persistence survey (n = 6577), 24.5% of patients reported discontinuing at least one antimuscarinic (AM) during the previous 12 months, mainly because of unmet treatment expectations (45.4%).¹⁶

OAB is a chronic medical condition, and patients deserve to be informed about the limitations of treatment and may need expert help in achieving realistic clinical and quality of life outcomes. The efficacy of medications can be reinforced by involving the patient in her/his treatment. Patient satisfaction with treatment is directly related to fulfilment of positive expectations, which should be jointly agreed upon by the patient and the physician.¹⁷ Physician counselling reduces nonadherence by half but potential conflicts in the message delivered to the patient may have a negative impact on adherence rates.^{18,19} Communication skills matter; in a meta-analysis of 21 experimental interventions,²⁰ better patient adherence was obtained by physicians who had received communication skill training compared with non-trained physicians.

Patient ^a	Provider
Dry all the time	70% reduction in incontinent episodes
Void six times/day	20% reduction in frequency of voiding
No side effects	Side effects that can be mitigated
Simple treatment plan (easy to administer, low pill burden)	Treatment plan that promotes adherence

TABLE 1 Sample discrepancies between patient and provider expectations (Adapted from Ellsworth et al¹⁵)

^aVoids 20 times/day and experiences five incontinent episodes/day.

What expectations of treatment do patients have? In the CONTROL study,²¹ when asked about treatment outcomes, 58% of 620 patients reported “being dry” as the most important treatment outcome. In a study of 153 women with OAB from a tertiary urogynaecology clinic, 24.3% of patients expected a complete cure of all their symptoms, 55.5% a good improvement, 9.1% to be able to better cope with symptoms, and 11.1% any improvement, no matter how small.²² Approximately half of women with UUI indicated that they desired a >70% reduction in leakage episodes to consider prescription therapy effective.²³ In the SAFINA study, an open label trial of flexibly dosed fesoterodine,²⁴ use of the Self-Assessment Goal Achievement (SAGA) questionnaire resulted in disease-related goals being set by 263 women and 68 men. For 77% of women, an important goal was “to reduce the sudden need to rush to the bathroom”, for 66% it was to “reduce frequency of trips to the bathroom through the day”, for 12% “to reduce difficulty starting or maintaining a urinary stream”, and for 81% of incontinent patients “to reduce my urine leakage”.

From the available data, the majority of patients express expectations focusing on efficacy in the reduction of disease-related variables. Unmet treatment expectations, as much as intolerability or lack of effect, are frequent reasons for discontinuation of treatment, and satisfied patients are more likely to be persistent with treatment. However, patient expectations vary, and OAB patients should be informed about realistic treatment outcomes in order to cope with their condition.

2.2 | What do we learn from the multicriteria decision analysis model?

The efficacy and safety profiles of OAB drugs differ, as assessed in systematic reviews and meta-analyses,²⁵ but there are few head-to-head comparisons. Network meta-analyses allow comparison of multiple

OAB treatments by combining objective data from many studies into a single number for each drug on a given criterion; however, they do not consider the relative importance and clinical relevance of the effects concerning benefit and safety.^{26,27} Information on the relative efficacy of these medications that compares their benefits and adverse events (AEs) in the management of OAB would be useful.

The MCDA model is based upon a computer-based algorithm developed by the London School of Economics and accepted by the EMA as a robust method to compare the benefits and safety of medicinal products.⁶ MCDA models have been published and validated.^{6,28-30} By combining the input of published data, MCDA models assess the favourable and unfavourable effects of comparator drugs at licensed recommended doses. The procedure involves several stages: selection of criteria, parameters, factors and deciders; development of an effect tree; selection of the weighing methods to represent the importance of each beneficial and harmful (adverse) effect; validation of the results with different weights; and performance of a sensitivity analysis to test the robustness of the system. MCDA provides simple to interpret information for physicians. In graphical terms, the cumulative beneficial effects are shown in grey and the unfavourable effects (adverse effects) in black. The higher the column, the more effective or safe the drug is. The higher the bar, the better the benefit-safety ratio (Figure 1).

The MCDA model has been applied to OAB drug treatment, results of which have been recently published.³¹ The study assessed the benefit-safety profile of OAB drugs, using published data and clinical judgment to perform a sensitivity analysis of benefit vs safety for individual OAB symptoms. Efficacy and safety data from published RCTs of muscarinic antagonists, the β_3 agonist mirabegron, and the combination of an AM and β_3 agonist using the EAU Guidelines database as a starting point, coupled with a full literature search of trials, were used for this analysis. The benefits assessed

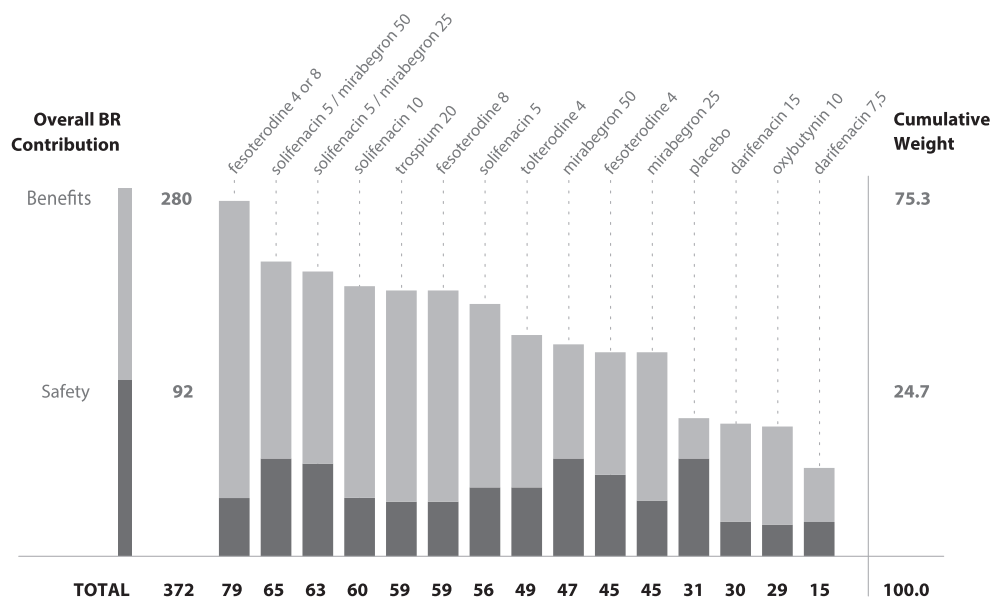


FIGURE 1 The overall weighted preference values for the OAB drugs is shown in the raw total. More grey indicates greater benefit, more black indicates greater safety. The weights shown in the white field are the sums of the benefit weights and the safety weights; their normalised values are given at the right. BR, benefit-risk. Reprinted from Chapple et al³¹ with permission of Elsevier

were urgency, UUI, frequency, and nocturia, as well as seven harmful effects: dry mouth, constipation, headache, dizziness, UTI, retention, and tachycardia (Figure 2).

When compared with other medications, fesoterodine with flexible dosing had the most favourable benefit-safety profile, followed by the combination of solifenacin and mirabegron. The authors noted that the benefit-safety profile for flexible dosing with fesoterodine was more marked than that seen with either 4 or 8 mg of fesoterodine, as well as that seen with fixed doses of solifenacin (5 or 10 mg) and of mirabegron (25 or 50 mg), but available data on flexible dosing with these medications were few. After sensitivity analysis, fesoterodine dosed flexibly with 4 or 8 mg remained the most preferred drug over a reasonable range of weights. A possible explanation for this finding is that the ability to dose up and down with fesoterodine maximises its benefits and safety for any individual patient. Fesoterodine is the only OAB drug with a consistent dose-response, and varying the dosage will vary the response.³² Interestingly, in this MCDA-mediated comparison the combination of solifenacin 5 mg and mirabegron 50 mg was less beneficial, but associated with better safety than flexibly dosed fesoterodine, suggesting that dose adaptation may be more beneficial for the patient than a combination of these two molecules with different modes of action and side effect profiles.

In conclusion, the MCDA model allows comparison of multiple treatment options, providing physicians with an easy-to-interpret benefit-safety analysis and helping their clinical decision-making.

2.3 | What can physicians expect from treatment for their patients?

Mathematical modelling has been used by Darekar et al³³ to predict outcomes from treatment using data from 12-week fesoterodine studies. Unsurprisingly, the greatest response to treatment was

predicted for patients who completed treatment and the lowest for those who withdrew because of AEs. The major problem with the model used here was the need to know the treatment response at four weeks a priori, and the complexity of the equation used in the study. Another method used pooled data from six fixed-dose, 12-week RCTs of fesoterodine 4, 8 mg, or placebo.³⁴ Overall, 70-80% of patients treated with fesoterodine (4 or 8 mg) experienced a 50% improvement in UUI at Week 12 and more than 50% of patients became dry with fesoterodine 8 mg. Some patients achieved 100% resolution in urgency episodes and more than half of fesoterodine-treated patients normalised (defined as <8 episodes/24 h) their daytime frequency at Week 12.

With respect to AEs, Wagg et al³⁵ analysed data from 6689 patients included in fesoterodine studies and found that resolution of urinary urgency by either 50% or 100% at Week 12 was associated with a reduction in the number of reported treatment-emergent AEs. This unexpected finding was observed for discontinuation rate, dry mouth, constipation, central nervous system (CNS) or cognitive adverse effects. Although not explained by the method it may be that patients may be less likely to express and to report AEs when the degree of benefit from treatment is either higher or reaches their expectations.

The impact of OAB drugs on cognitive function has recently become of concern, based upon analyses of retrospective observational studies which associate a high anticholinergic burden with an increased rate of dementia diagnosis.³⁶ Although there is a small association, there is evidence of patient concern.³⁷ While there are few direct data on the association of adverse cognitive effects of OAB drugs, the different OAB drugs have different propensities to penetrate the CNS. Lipophilicity and molecular size determine how easily AMs cross the blood-brain barrier and some are removed from the brain via an active transport mechanism, the permeability glycoprotein (P-gp). AM drug concentrations in

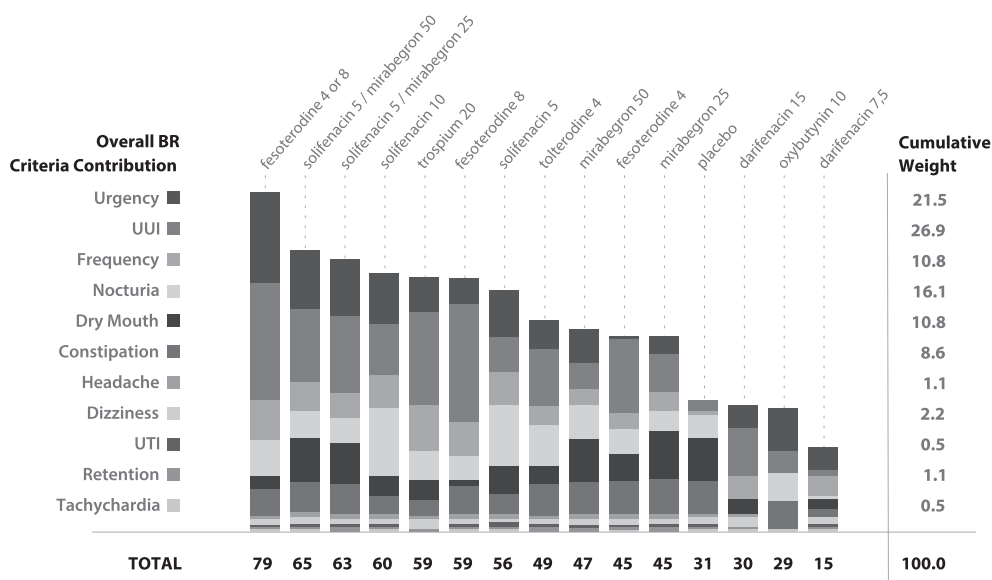


FIGURE 2 Contributions to the totals by each of the 11 effects. The four upper sections show the magnitude of the benefits, and the rest show safety. BR, benefit-risk; UTI, urinary tract infection; UUI, urgency urinary incontinence. Reprinted from Chapple et al³¹ with permission of Elsevier

rat plasma, brain and cerebro-spinal fluid have been measured.³⁸ Brain penetration was low for AMs that are P-gp substrates, such as 5-HMT (fesoterodine), trospium and darifenacin, but significant for those which are not, including oxybutynin, solifenacin and tolterodine. The clinical impact of fesoterodine on cognitive function has been studied in three prospective clinical trials. Kay et al³⁹ used a cognitive test to evaluate cognitive function in cognitively intact older adults (age: 65-85 years) and demonstrated that there was no relevant effect at either the 4 mg or 8 mg dose. In the SOFIA study, Wagg et al⁴⁰ assessed cognitive function of elderly (≥ 65 years) OAB patients by using the Mini-Mental State Examination (MMSE). No meaningful changes were observed after 12 weeks. Likewise, in the Vulnerable Elders study, Dubeau et al⁴¹ found no deterioration in mean MMSE scores from baseline to Week 12 in either the fesoterodine or the placebo group. These studies are limited by their short-term nature, and no longer term studies exist. The current European Urology Association guidelines note caution in the use of long-term antimuscarinic agents in older people.⁴² In the LUTS-FORTA classification,⁴³ fesoterodine was the only OAB drug to be classified as B (beneficial). No OAB drug was classified as A, several drugs were classified as C (darifenacin, mirabegron, oxybutynin ER, solifenacin, tolterodine, trospium) and two drugs, oxybutynin IR and propiverine, were classified D. Conclusions from this study were limited by the availability of published relevant data.

The take-home messages drawn from the symposium are:

1. OAB is a highly prevalent undertreated storage symptom complex, with urgency as the pivotal symptom;
2. Patients are often reluctant to report their problems and may have unrealistic expectations of the available treatments;
3. Physician support is an important aspect of treatment, and good communication skills coupled with an evidence-informed approach to care will improve adherence to OAB treatment;
4. MCDA modelling provides valuable information by comparing the benefit-safety profiles of OAB drugs;
5. Fesoterodine is an effective drug; and when compared with other medications, flexibly dosed fesoterodine has the most favourable benefit-safety profile;
6. The importance of a personalised approach to the management of patients with OAB.

DISCLOSURES

Christopher Chapple has received honoraria or grants from Astellas for a scientific study/trial as a researcher, author, meeting participant, speaker, and consultant/advisor; from Bayer Schering Parma AG as a consultant/advisor; from Galvani Bioelectronics (GSK) as a consultant/advisor; from Ipsen for a scientific study/trial as a researcher; from Lupin Limited as a meeting participant and speaker; from Pfizer as a meeting participant and speaker; from Pierre Fabre as a consultant/advisor; from Recordati for a scientific study/trial as a researcher, author, meeting participant and speaker; from Sun Pharmaceutical as a meeting participant

and speaker; from Symimetics as a consultant/advisor for a patent; from Taris Biomedical as a consultant/advisor and from Urovant Sciences as a consultant/advisor.

Matthias Oelke has received honoraria from Apogepha Arzneimittel as a speaker and trial participant; from Astellas as an advisor, speaker, and trial participant (research grant); from Bayer Healthcare as a speaker; from Duchesnay as a speaker; from Pierre Fabre as a speaker; from Pfizer as an advisor, speaker and trial participant (research grant) and from Sun Pharmaceutical as a speaker.

Adrian Wagg has received honoraria from Astellas as a speaker and for consulting; from Essity Health & Hygiene AB for consulting, research and as a speaker; from Pfizer Corporation for consulting and research grants and honoraria from Pierre Fabre as a speaker and for consultancy.

Ian Milsom has received honoraria for lectures from Astellas, Essity, Allergan and Pierre Fabre.

FUNDING INFORMATION

Pierre Fabre Laboratories sponsored the symposium and the writing assistance (by Azimut, Castres, France).

ORCID

Ian Milsom  <https://orcid.org/0000-0002-0400-5509>

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How to cite this article: Milsom I, Wagg A, Oelke M, Chapple C. Which drugs are best for overactive bladder? From patients' expectations to physicians' decisions. *Int J Clin Pract.* 2021;75:e13870. <https://doi.org/10.1111/ijcp.13870>