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Benefit-Risk Evaluation of Tolterodine 4 mg and Fesoterodine Fixed and Flexible Dosing

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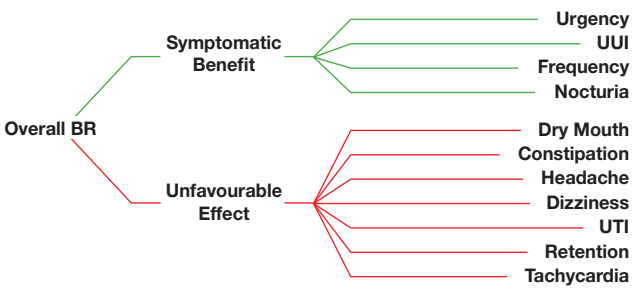
1 Introduction

- Clinicians use the most recent available clinical data to select and optimise treatment options for overactive bladder (OAB). These data are often driven by safety or efficacy, with limited published benefit-risk (BR) assessments available. Fragmented data can cause difficulty in quantifying the BR profile of medicines,[1-3] leading to challenges in clinical decision making.
- Simple tools are needed to ascertain the BR of individual medicines. This is of specific concern for clinicians selecting an OAB treatment because several options are available with differing mechanisms of action and efficacy and safety profiles.[4]
- Computer-based models may be used to assess BR profiles.[3,5,6] These models combine the best available evidence with clinical judgement about the data to provide valid and reliable decision-making guides.
- A multicriteria decision analysis (MCDA) computer-based model assessed the BR profiles of 12 OAB drug-treatment options; 3 profiles associated with fesoterodine (FES) and tolterodine (TOL) are reported here.

2 Methods

- Efficacy and safety data from published, randomised, placebo (PBO)-controlled trials of TOL and FES were used to populate an MCDA model.
- Using European Medicines Agency–accepted methodology,[7] data were evaluated against the 4 symptomatic benefits and 7 unfavourable effects judged most likely to affect patient outcomes **(Figure 1)**.

Figure 1. Effects Tree for Determining the Relative BR of OAB Medicines



BR=benefit-risk; OAB=overactive bladder; UTI=urinary tract infection; UUI=urge urinary incontinence.

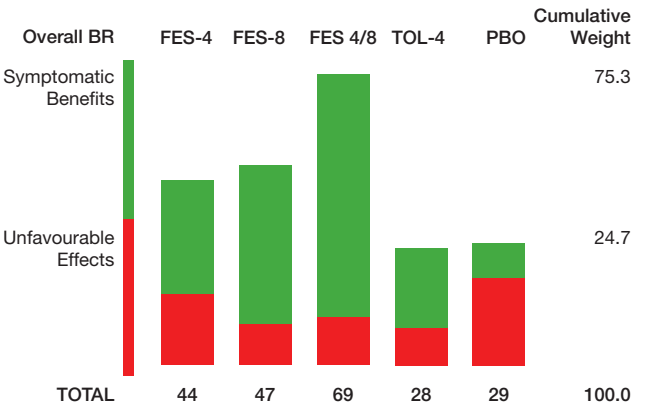
- TOL 4 mg and FES 4- and 8-mg fixed doses and a FES flexible-dosing regimen (4 or 8 mg) were analysed.
- Using available clinical evidence or assessment, each criterion was scored from 0 to 100 (ie, least preferred to most preferred data points) for the full model. Values in between those points were assigned relative values in the range in the same relative positions as given by the data.
- Data were weighted in the full model by (i) relative weighting of the criteria for symptomatic benefit criteria, (ii) relative weighting comparing swings for symptomatic benefit criteria, and (iii) relative weighting of highest-weighted symptomatic benefit criterion against highest-weighted unfavourable effect criterion.
- Sensitivity analyses were performed by varying the criteria weighting to determine if overall results were affected.
- Data are quantitative; no statistical comparisons were made.

3 Results

Comparison of BR profiles

- The model showed a favourable BR profile for FES flexible dosing compared with TOL and FES single-dose interventions **(Figure 2)**.

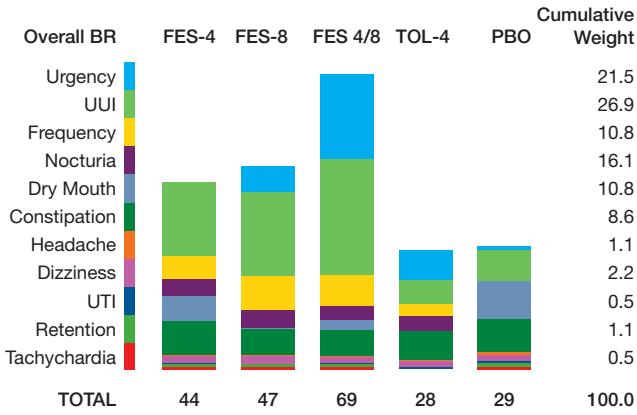
Figure 2. Overall BR Profile of TOL 4 mg, FES 4 and 8 mg, and FES Flexible Dosing (4 or 8 mg) Treatment Options and PBO



Higher scores for individual criteria equate to greater benefits or less risk; that is, more green represents more symptomatic benefit and more red represents less risk/unfavourable effect.
BR=benefit-risk; FES-4=fesoterodine 4 mg; FES 4/8=fesoterodine flexible dosing (4 or 8 mg); FES-8=fesoterodine 8 mg; PBO=placebo; TOL-4=tolterodine 4 mg.

- The model allowed analysis of the BR profile of each drug by individual symptomatic benefit and unfavourable effect criteria **(Figure 3)**. The most favourable BR profiles were observed for urge urinary incontinence (UUI) and urgency with FES flexible dosing.
- PBO data from available clinical studies for the 12 treatment options illustrated the safety advantages of all other assessed treatment options compared with PBO **(Figure 3)**.

Figure 3. BR Profiles of TOL 4 mg, FES 4 and 8 mg, and FES Flexible Dosing (4 or 8 mg) by Individual Symptomatic Benefit and Unfavourable Effect Criteria



BR=benefit-risk; FES-4=fesoterodine 4 mg; FES 4/8=fesoterodine flexible dosing (4 or 8 mg); FES-8=fesoterodine 8 mg; PBO=placebo; TOL-4=tolterodine 4 mg; UTI=urinary tract infection; UUI=urge urinary incontinence.

Comparison of treatment advantages and disadvantages

- The model allowed comparison of the advantages and disadvantages of the OAB treatments. In this example, FES flexible dosing outperformed TOL 4 mg on UUI, urgency, frequency, and retention; TOL did not outperform FES flexible dosing on any effect **(Figure 4)**.

Figure 4. Comparison of FES Flexible Dosing (4 or 8 mg) With TOL 4 mg

Model Order	Cumulative Weight	Difference	Weighted Difference	Sum
UUI	26.9	79	21.2	21.2
Urgency	21.5	61	13.1	34.3
Frequency	10.8	43	4.6	38.9
Dry Mouth	10.8	24	2.6	41.5
Retention	1.1	69	0.7	42.2
Headache	1.1	30	0.3	42.5
Tachychardia	0.5	41	0.2	42.7
UTI	0.5	0	0.0	42.7
Dizziness	2.2	–2	–0.0	42.7
Nocturia	16.1	–3	–0.5	42.2
Constipation	8.6	–12	–1.0	41.2
TOTAL	100.0		41.2	

Purple bars indicate advantages of FES flexible dosing (4 or 8 mg), orange bars indicate advantages of TOL 4 mg. Green highlight indicates **Symptomatic Benefit**; red highlight indicates **Unfavourable Effect.**
FES=fesoterodine; TOL=tolterodine; UUI=urge urinary incontinence; UTI=urinary tract infection.

Sensitivity analyses

- The model was robust in sensitivity analyses, confirming that results were relatively unchanged even with significant changes in weighting or to the published evidence.

4 Conclusions

- **The full MCDA model was applied to assess the BR profiles of different OAB treatments and to compare profiles across treatments. The model permits breakdown of the overall BR profile by individual symptomatic benefit and unfavourable effect criteria for each drug, allowing identification of the criteria providing the greatest and least benefit for each drug.**
- **Using the MCDA model, FES flexible dosing for OAB had a more favourable BR profile than fixed-dose TOL and FES.**
- **The MCDA model is a useful output that can compare multiple treatment options, providing clinicians with an easy-to-interpret BR analysis to help inform clinical decision making.**

5 References

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