

Estimating the Quality of Life Impact of Tolterodine and Tamsulosin Treatment in Men with Lower Urinary Tract Symptoms and Overactive Bladder

Verheggen BG¹, Treur MJ¹, Heeg BMS¹, Botteman MF², Trocio JN³

¹Pharmerit Europe, Rotterdam, Netherlands, ²PharMerit North America LLC, Bethesda, MD, USA, ³Pfizer Inc, New York, NY, USA

1 Abstract

Objective: A randomized clinical trial (TIMES) demonstrated that combination therapy with tolterodine extended release (ER) plus tamsulosin for 12 weeks provides clinical benefits over monotherapy with either agent or placebo in men with moderate to severe lower urinary tract symptoms (LUTS) and overactive bladder. However, the TIMES study did not report the impact of these therapies on utility. We developed a statistical model to estimate the utility and quality-adjusted life-years (QALYs) associated with the various TIMES therapies.

Methods: The statistical model was developed using urinary tract symptoms and quality of life (SF-12) data collected from 9416 males participating as part of a separate epidemiologic survey (EpiLUTS). The model was a multinomial regression, which predicted the level of responses to each of the 12 domains of the SF-12. The predictors were daytime and nighttime urinary frequency, urgency episodes, urgency urinary incontinence and International Prostate Symptom Scores (IPSS). This regression was then used to predict SF-12 scores of the TIMES patients, based on the observed mean symptoms values in this study. Next, based on published regression algorithms, these predicted SF-12 answers were transformed into EQ-5D utility scores, from which QALYs were calculated.

Results: IPSS score and number of urgency episodes in 24 hours had the strongest impact on overall utility, whereas nighttime and especially daytime micturition frequency had less impact. At week 12, utility scores for placebo, tolterodine monotherapy, tamsulosin monotherapy, and combination therapy were 0.657, 0.684, 0.679 and 0.701, respectively. Corresponding QALYs over 12 weeks were 0.143, 0.146, 0.146 and 0.148. Thus, combination therapy resulted in the highest incremental QALYs, saving 0.005 QALYs vs. placebo, 0.002 vs. tolterodine, and 0.003 vs. tamsulosin.

Conclusion: Combination therapy with tolterodine ER plus tamsulosin results in the highest predicted utility and QALY gains compared to placebo or monotherapy with either agent.

2 Background

- Lower urinary tract symptoms (LUTS) encompass symptoms related to overactive bladder (OAB) due to detrusor overactivity, and bladder outlet obstruction due to benign prostatic hyperplasia (BPH). These symptoms may co-exist in male patients.
- In a randomized clinical trial (the "TIMES" study), 851 male patients with co-existing bladder and prostate symptoms were treated for 12 weeks with placebo, 4mg extended release (ER) tolterodine, 0.4mg tamsulosin, or a combination of the last two therapies.(1)
- In this study, combination therapy was shown to be tolerable and more effective than monotherapy with either agent. However, the impact of these therapies on utility was not one of the outcomes in the TIMES study.

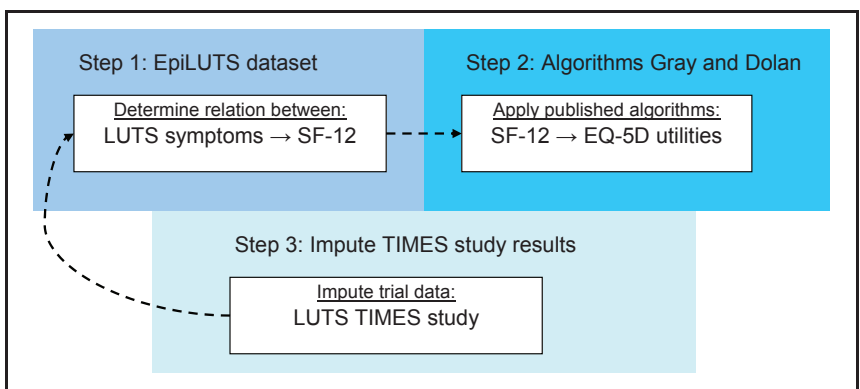
3 Objective

- To estimate the utility and quality-adjusted life-years (QALYs) associated with the various TIMES therapies via a statistical model in men with LUTS suggestive of both bladder and prostate symptoms.

4 Methods

- The TIMES study did not collect utility data. However, it reported information on urgency episodes, urgency urinary incontinence, day- and nighttime urinary frequency and IPSS
- Thus, for the present analysis, it was necessary to first establish the statistical relationships between these clinical outcomes, quality of life measures and utilities, as observed in a separate data set.
- For this purpose, a dataset on LUTS symptoms and SF-12 from 9416 males who participated in an epidemiologic survey (EpiLUTS) was used.
- Specifically, data on the LUTS symptoms were used to predict SF-12 scores from the EpiLUTS patients. Next, the predicted SF-12 scores were transformed into utilities using a procedure detailed below.
- Finally, the results of the TIMES in terms of LUTS symptoms for each treatment option were imputed into these associations to predict the corresponding utilities.
- Figure 1 presents the various steps involved in this process.

Figure 1. Schematic overview: applied methodology to link LUTS to utilities



Step 1

- Patient level urgency episodes, urgency urinary incontinence, day- and nighttime urinary frequency and IPSS from the EpiLUTS were used to predict the probability for each answer to each of the 12 items of the SF-12.
- This resulted in a series of 12 multinomial logit regression models to estimate the relation between urinary tract symptoms and the SF-12. See Figure 2 for mathematical model formulation of the 'General Health' question of the SF-12 (which has 5 answering options: excellent, very good, good, fair, poor). Similar models were fitted for the other SF-12 questions.

Figure 2. Mathematical equations of the multinomial model. Example for one of the SF-12 questions with five answering options

$$P[SF_i = j] = \begin{cases} \frac{1}{1 + \sum_{j=2}^5 x_j \cdot \beta^j} & j = 1 \\ P[qD_i = 1] \cdot \exp(x_j \cdot \beta^j) & j = 2, \dots, 5 \end{cases}$$

$$x_j = (1 \ln[DF_i + 1] \ln[NF_i + 1] URG_i^1 \dots URG_i^4 INC_i^1 \dots INC_i^5 IPSS_i)$$

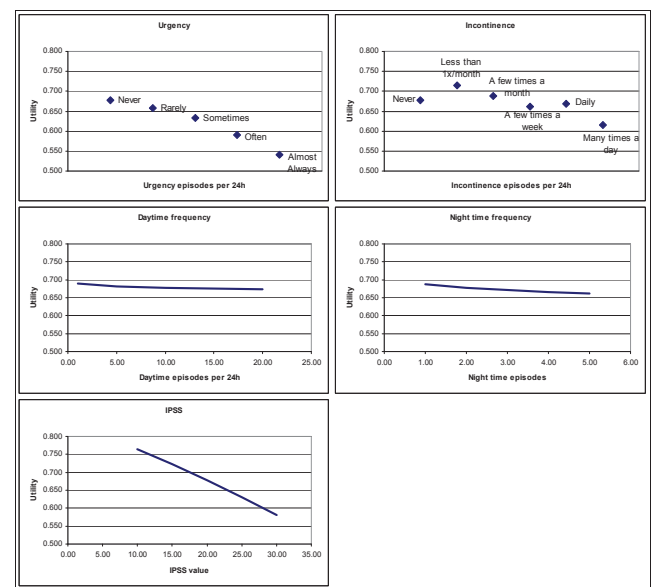
$$\beta^j = (\beta_0^j \dots \beta_{12}^j)$$

SF_i = SF-12 answer given by patient *i*
j = answering option
 DF_i = daytime urinary frequency of patient *i*
 NF_i = nighttime urinary frequency of patient *i*
 URG_i¹⁻⁴ = dummy variables to reflect answer given to categorical urgency question by patient *i*
 INC_i¹⁻⁵ = dummy variables to reflect answer given to categorical urgency urinary incontinence question by patient *i*
 IPSS_i = International Prostate Symptom score of patient *i*

Step 2

- Responses to the SF-12 can be converted into utilities using a number of methods. This was accomplished using published (multinomial) regression algorithms by Gray *et al*, who links SF-12 responses to EQ-5D health states (2), which can then in turn be converted into a single utility value using Dolan *et al*.(3)
- Having defined the indirect association between five LUTS symptoms and utility, the impact of varying each of these five symptoms individually on the utility score is determined (Figure 3).

Figure 3. Impact of separate LUTS symptoms on utility



- Utilities are most sensitive to changes in urgency episodes and IPSS (Figure 3).

Step 3:

- To estimate utility values for patients enrolled in the TIMES study, efficacy data on LUTS for patients treated with placebo, tolterodine, tamsulosin, or combination therapy were extracted from the TIMES study, and imputed in the mathematical model (Table 1).

Table 1. TIMES study results: Baseline urinary tract symptoms and observation after 12 weeks (incremental values represent adjusted mean changes)

Symptom	Base line	Placebo		Tolterodine		Tamsulosin		Combination	
		Wk 12	Change	Wk 12	Change	Wk 12	Change	Wk 12	Change
24h frequency	11.86	10.45	-1.41	10.19	-1.67	10.11	-1.75	9.32	-2.54
Nighttime frequency	2.02	1.63	-0.39	1.67	-0.35	1.49	-0.53	1.34	-0.59
Urgency Inc episodes	0.98	0.67	-0.31	0.15	-0.83	0.28	-0.70	0.10	-0.88
Urgency episodes	7.33	4.79	-2.54	4.59	-2.74	4.99	-2.34	4.00	-3.33
IPSS	20.00	13.81	-6.19	13.15	-6.85	12.11	-7.89	11.98	-8.02

5 Results

- When TIMES study results were imputed in the multinomial model, utility scores at 12 weeks for placebo, tolterodine monotherapy, tamsulosin monotherapy, and combination therapy were 0.657, 0.684, 0.679 and 0.701, respectively (Table 2).
- Corresponding QALYs over 12 weeks for respectively placebo, tolterodine, tamsulosin and combination therapy were 0.143, 0.146, 0.146 and 0.148. Thus, combination therapy resulted in the highest incremental QALYs, saving 0.005 QALYs vs. placebo, 0.002 vs. tolterodine, and 0.003 vs. tamsulosin (Table 2).

Table 2. Utility values at baseline and week 12 and QALY calculations

	Placebo	Tolterodine	Tamsulosin	Combination
Utility Baseline	0.586	0.586	0.586	0.586
Utility wk 12	0.657	0.684	0.679	0.701
QALYs	0.143	0.146	0.146	0.148
QALYs Gained with Combination	0.005	0.002	0.003	

- QALY differences resulting from TIMES study observations are mainly explained by higher efficacy of combination therapy on IPSS and urgency episodes compared to the other treatment alternatives.

6 Limitations

- The association between LUTS symptoms and patient utility was estimated indirectly through a number of associations.
- TIMES study results on urgency and urgency urinary incontinence had to be converted to categorical urgency and urgency urinary incontinence answers of EpiLUTS.
- Currently, no uncertainty was included in the model. The main reason was that the correlation between LUTS symptoms and covariance were unknown.

7 Conclusions

- Combination therapy with tolterodine ER plus tamsulosin is predicted to result in the highest utility and QALY gains compared to placebo or monotherapy with either agent.

8 References

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This study was sponsored in part by Pfizer Inc. Editorial support was provided by SciFor.

This poster was presented at the ISPOR 11th Annual European Congress; November 8-11 2008; Athens Greece