



## Voiding Dysfunction

# Number of Daytime Micturitions and Volume Voided per Micturition in the Evaluation of Efficacy of Drugs for Overactive Bladder: Findings from Randomized Clinical Trials

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### Abstract

**Objective:** To analyze the relationship between mean volume voided per micturition and number of daytime micturitions.

**Methods:** We reviewed data from randomized clinical trials on the medical treatment of overactive bladder published in the international literature between 1997 and 2004. Fourteen studies including data on these two parameters were identified.

**Results:** Six studies compared tolterodine with placebo, two tolterodine and oxybutynin with placebo, two tolterodine with oxybutynin, two solifenacin and tolterodine with placebo, one oxybutynin CR with oxybutynin IR, and one different doses of solifenacin. The correlation between the percent change in the mean voided volume and in the number of daytime micturitions was assessed using the Spearman rank correlation coefficient ( $r$ ), with  $r = -0.67$  for all the studies. For groups of patients treated with each drug, we found  $r = -0.09$  for oxybutynin,  $r = -0.59$  for tolterodine,  $r = -0.85$  for solifenacin, and  $r = -0.34$  for placebo.

**Conclusion:** The results of this analysis suggest that in the evaluation of the efficacy of a drug for overactive bladder, the mean volume voided per micturition may be a useful measure of efficacy.

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## 1. Introduction

According to the International Continence Society recommendations, overactive bladder syndrome is defined as urgency with or without urge incontinence, usually with frequency and nocturia [1]. Although there is agreement about the presence of these symptoms, it remains unclear how they are related to other parameters, such as volume voided per micturition. This parameter is important for assessing the effectiveness of treatments.

In recent years interest has focused on the use of volume voided per micturition as the best indicator of efficacy of medical treatment for overactive bladder. Studies have suggested that the volume voided per micturition, a semi-objective parameter, may be less affected by placebo than the number of micturitions per day [2]. An increase in the volume voided per micturition should indicate that the bladder capacity is greater at the time of micturition and any increase in volume voided per micturition should lead to an improvement in the frequency of micturition.

A recent Korean study on 41 men and 63 women found a statistically significant correlation ( $r < 0.43$ ) between mean volume per micturition and number of daytime micturitions [3]. The mean volume voided per micturition has been used in randomized clinical trials to assess the efficacy of medical treatments. For example, Chapple et al. [4] used this measure to assess the efficacy of solifenacin succinate in a phase III trial. The efficacy variables included change from baseline in the mean number of urgency, incontinence, and urge-incontinence episodes; change from baseline in micturitions per 24 h; and mean volume per micturition. The mean volume per micturition was significantly higher with all active treatments [4], confirming the greater efficacy of solifenacin succinate on mean number of urgency, incontinence, and urge-incontinence episodes.

Despite these suggestions, the relation between total daytime voided volume and number of daytime micturitions is not completely clear. To gain a better understanding of this issue, we reviewed reports of randomized clinical trials on the medical treatment of overactive bladder, published in the international literature between 1997 and 2004, that presented data for mean volume per micturition and number of daytime micturitions.

## 2. Methods

Eligible for this analysis were randomized clinical trials on the medical treatment of overactive bladder published in English

in peer-reviewed journals between 1997 and 2004 and including information on number of daytime micturitions and volume voided per micturition as primary or secondary end points. Studies were identified by reviewing reference lists in relevant publications and by a MEDLINE search using the keywords "randomized clinical trials" and "urinary incontinence" and calendar period (1997–2004) as the limit.

Reviewers (FP and SC) decided which trials were potentially eligible on the basis of information available in the abstracts published in MEDLINE or data reported in papers available in this phase of the study. A paper was defined potentially eligible if it was a randomized clinical trial comparing the efficacy of medical treatments for overactive bladder and if it indicated as primary or secondary end points the effect of treatment on number of micturitions per day and/or volume voided per micturition.

Seventeen studies were identified [2,4–19]. All full papers identified as eligible by at least one reviewer were read. After careful reading of papers three reports were not included because they lacked precise information on the number of micturitions per day or volume voided per micturition [7–9].

### 2.1. Data analysis

For each trial the two reviewers independently identified the number of subjects treated in each group and the mean number of daytime micturitions and volume voided per micturition at baseline and at the end of treatment. Disagreements in the interpretation of published data were resolved by discussion between the reviewers.

We computed the difference between the baseline and end-of-study values for the mean number of daytime micturitions and volume voided per micturition for each treatment group. In some cases, this difference was published in the original paper. These two parameters were chosen because they are commonly reported as end points in studies of medical treatments of overactive bladder. In addition, we computed for each study group the percent change in the number of daytime micturitions and mean volume voided per micturition (difference between baseline and end-of-study values divided by the baseline values). Spearman rank correlation coefficient ( $r$ ) was used to quantify the relationship between the percent change in the total daytime voided volume and the percent change in the number of daytime micturitions.

Finally, for all the studies and for each drug or placebo, the weighted mean (based on the sample size of each study) of the difference between baseline and end-of-study values and percent change were computed for number of micturitions and mean volume voided per micturition.

## 3. Results

Table 1 shows the main characteristics of the trials examined. The number of patients included ranged from 94 to 1529 (median: 502). Six studies compared tolterodine with placebo, two tolterodine and oxybutynin with placebo, two tolterodine with oxybutynin, two solifenacin and tolterodine with placebo,

**Table 1 – Characteristics of the trials examined**

Study	Sample size	Drugs investigated	Placebo	Duration of study
Jonas et al. 1997 [5]	242	tolterodine 1 mg bid (99 pts) tolterodine 2 mg bid (99 pts)	yes (44 pts)	4 wk
Abrams et al. 1998 [6]	293	oxybutynin 5 mg tid (118 pts) tolterodine 2 mg bid (118 pts)	yes (57 pts)	
Drutz et al. 1999 [10]	277	oxybutynin 5 mg tid (112 pts) tolterodine 2 mg bid (109 pts)	yes (56 pts)	12 wk
Millard et al. 1999 [11]	316	tolterodine 1 mg bid (123 pt) tolterodine 2 mg bid (129 pts)	yes (64 pts)	12 wk
Chancellor et al. 2000 [12]	1022	tolterodine 2 mg bid (514 pts)	yes (508 pts)	12 wk
Van Kerrebroeck et al. 2001 [13]	1529	tolterodine ER 4 mg (507 pts) tolterodine IR 2 mg bid (514 pts)	yes (508 pts)	12 wk
Jacquetin and Wyndaele 2001 [14]	251	tolterodine 1 mg bid (97 pts) tolterodine 2 mg bid (103 pts)	yes (51 pts)	4 wk
Malone-Lee et al. 2001 [15]	378	oxybutynin 5 mg bid (188 pts) tolterodine 2 mg bid (190 pts)	no	10 wk
Barkin et al. 2004 [16]	94	oxybutynin CR 15 mg (53 pts) oxybutynin IR 15 mg (41 pts)	no	6 wk
Giannitsas et al. 2004 [17]	107 (only women)*	oxybutynin 15 mg tolterodine 2 mg bid	no	6 wk
Chapple et al. 2004 [4]	192	solifenacin 2.5 mg (40 pts) solifenacin 5 mg (37 pts) solifenacin 10 mg (33 pts) solifenacin 20 mg (34 pts)	yes (36 pts)	4 wk
Chapple et al. 2004 [18]	1033	tolterodine 2 mg bid (37 pts) solifenacin 5 mg (266 pts) solifenacin 10 mg (264 pts) tolterodine 2 mg bid (250 pts)	yes (253 pts)	12 wk
Landis et al. 2004 [2]	381 (only serious cases)	tolterodine 4 mg (171 pts)	yes (210 pts)	12 wk
Cardozo et al. 2004 [19]	907	solifenacin 5 mg (299 pts) solifenacin 10 mg (307 pts)	yes (301 pts)	12 wk

\* Cross-over study.

one oxybutynin CR with oxybutynin IR, and one different doses of solifenacin. The duration of treatments ranged from 4 to 12 wk.

Table 2 lists the results in terms of the difference between baseline and end-of-treatment values for the number of micturitions and mean volume voided per micturition according to treatment allocation. The correlation coefficients between the percent change in the total daytime voided volume and the percent change in the number of daytime micturitions was assessed. Considering all the trials, the coefficient was  $r = -0.67$  (95% CI:  $-0.82$  to  $-0.46$ ). The coefficients were  $r = -0.09$  (95% CI:  $-0.84$  to  $+0.79$ ) for oxybutynin,  $r = -0.59$  (95% CI:  $-0.84$  to  $-0.13$ ) for tolterodine,  $r = -0.85$  (95% CI:  $-0.98$  to  $-0.37$ ) for solifenacin, and  $r = -0.34$  (95% CI:  $-0.80$  to  $+0.38$ ) for placebo. The lack of a significant association for oxybutynin and placebo may be in part due to the low number of trials available.

#### 4. Discussion

The general results of this descriptive analysis indicate that in randomized clinical trials there is

an appreciable inverse relationship between the efficacy of medical treatment for symptoms of overactive bladder measured as the number of micturitions per day or mean volume voided per micturition. This finding was consistent when we considered separately the different treatments or durations of treatments, with the sole exception of analysis for oxybutynin trials, which may be in part due to the low number of trials.

These results are in line with previously published data. For example, Ku et al. [3] reported a strong correlation between mean voided volume per micturition and number of daytime micturitions. Van Brummen et al. [20] investigated the association between overactive bladder symptoms and objective parameters from patients' bladder diaries and conventional filling cystometry. Based on a univariate analysis, they found that frequency was associated with lower micturition and bladder sensation volumes. A multivariate analysis revealed that frequency was associated with a lower maximum volume voided and mean volume voided per micturition, based on data from bladder diaries, and was also associated with lower sensation volumes, as measured by filling cystometry. A comparison of

Table 2 – Results

Study	No. micturition per day*		Mean volume voided per micturition (ml)*	
	No. (SD)	Percent change	Mean (SD)	Percent change
<b>Oxybutynin</b>				
Abrams et al. 1998 [6]	-2.3 (2.7)	-20	+47 (58)	+31
Drutz et al. 1999 [10]	-2.0 (2.3)	-17	+50 (43)	+34
Malone-Lee et al. 2001 [15]	-1.7	-15	+34	+23
Giannitsas et al. 2004 [17]	-0.8	-9	+43	+22
Barkin et al. 2004 [16]				
Oxybutynin IR	-2.4 (n.a.)	-22	+40 (n.a.)	+18
Oxybutynin CR	-1.8 (n.a.)	-16	+25 (n.a.)	+14
Total	-2.0	-17.3	+40.0	+25.9
<b>Tolterodine</b>				
Jonas et al. 1997 [5]				
2 mg	-1.4 (2.4)	n.a.	+20 (45)	n.a.
4 mg	-1.7 (2.4)	n.a.	+20 (38)	n.a.
Abrams et al. 1998 [6]	-2.7 (3.8)	-21	+38 (54)	+27
Drutz et al. 1999 [10]	-2.0 (2.5)	-17	+34 (41)	+21
Millard et al. 1999 [11]				
2 mg	-2.3 (3.0)	-20	+27 (41)	+18
4 mg	-2.3 (2.1)	-21	+36 (50)	+23
Chancellor et al. 2000 [12]	-1.7 (3.3)	-15	+29 (47)	+21
Malone-Lee et al. 2001 [15]	-1.7	-15	+33	+22
Van Kerrebroeck et al. 2001 [13]				
2 mg	-3.3 (4.4)	-30	+29 (47)	+21
4 mg	-3.5 (4.9)	-32	+34 (51)	+24
Jacquetin and Wyndaele 2001 [14]				
2 mg	-1.4 (2.8)	-13	+20 (42)	+13
4 mg	-1.4 (4.3)	-13	+19 (46)	+12
Chapple et al. 2004 [4]	-1.8 (n.a.)	-15	+15 (n.a.)	+14
Chapple et al. 2004 [18]	-1.9 (3.0)	-16	+24.4 (49.2)	+17
Landis et al. 2004 [2]**	-1.9 (n.a.)	-17.4	+27	+20
Giannitsas et al. 2004 [17]	-0.9	-11	+41	+21
Total	-2.4	-21.6	+29.0	+20.7
<b>Solifenacil</b>				
Chapple et al. 2004 [4]				
2.5 mg	-1.5 (n.a.)	-12	+19.9 (n.a.)	+20
5 mg	-2.2 (n.a.)	-18	+38.0 (n.a.)	+28
10 mg	-2.5 (n.a.)	-21	+43.2 (n.a.)	+35
20 mg	-2.8 (n.a.)	-23	+64.7 (n.a.)	+45
Chapple et al. 2004 [18]				
5 mg	-2.2 (2.9)	-18	+32.9 (47.7)	+22
10 mg	-2.6 (3.2)	-21	+39.2 (50.5)	+27
Cardozo et al. 2004 [19]				
5 mg	-2.4 (n.a.)	n.a.	+31 (n.a.)	n.a.
10 mg	-2.8 (n.a.)	n.a.	+36 (n.a.)	n.a.
Total	-2.5	-19.2	+35.3	+26.0
<b>Placebo</b>				
Jonas et al. 1997 [5]				
Abrams et al. 1998 [1]	-0.6 (2.0)	n.a.	+11 (35)	n.a.
Millard et al. 1999 [11]	-1.6 (3.6)	-10.5	+6 (42)	+7
Drutz et al. 1999 [10]	-1.4 (2.3)	-12	+10 (47)	+6
Chancellor et al. 2000 [12]	-1.1 (2.9)	-10	+12 (41)	+8
Van Kerrebroeck et al. 2001 [13]	-1.2 (2.9)	-11	+14 (41)	+10
Jacquetin and Wyndaele 2001 [14]	-2.2 (4.0)	-19	+14 (41)	+10
Chapple et al. 2004 [4]	-1.2 (2.7)	-10	+7 (40)	+5
Chapple et al. 2004 [18]	-1.0 (n.a.)	-9	+9.7 (n.a.)	+14
Landis et al. 2004 [2]**	-1.2 (3.3)	-10	+7.4 (36.3)	+5
Giannitsas et al. 2004 [17]	-0.4 (n.a.)	-5	+2.9 (n.a.)	+2

Table 2 (Continued)

Study	No. micturition per day <sup>*</sup>		Mean volume voided per micturition (ml)	
	No. (SD)	Percent change	Mean (SD)	Percent change
Cardozo et al. 2004 [19]	n.a.	n.a.	+10.7 (n.a.)	n.a.
Total	-1.4	-12.4	+10.9	+7.9
Overall total	-2.1 (10.3)	-18.2	+25.5 (155.0)	+17.9

<sup>\*</sup> Difference between the baseline and the end of the study.  
<sup>\*\*</sup> Data based on median.

the efficacy of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome suggested similar quantitative effect of these treatments on mean volume voided per micturition and number of micturitions per day [21]. Similar findings were noted, although not formally analyzed, in a meta-analysis and systematic review [22,23].

Potential limitations of this analysis should be considered. First, we only considered published data, and some studies reported results only in terms of the number of micturitions per day. In addition, we only considered summary statistics from the original papers. It is difficult to evaluate the main strengths or weakness of the studies considered, thus we were not able to consider only those studies of the highest quality, but it should be emphasized that we considered only randomized trials. It would be useful to confirm the findings of Ku et al. [3] in one or more of the trials using individual data. In addition, selective bias in the presentation of the results cannot be excluded. However, the results were largely consistent across trials with different numbers of patients and in patients treated with placebo or the various drugs.

Animal studies have suggested that the effect of tolterodine on micturition is sex specific [24]. Likewise, a recent study on 1152 volunteers without any voiding complaint showed that the volume per micturition decreased significantly with age in both genders, but particularly in men [25]. Thus, it is possible that the number of micturitions may also vary with age and sex. Published studies, however, offer scant information on this point, and we were therefore not able to analyze these two factors. The one study that included only women [17] reported results similar to those obtained in studies involving both genders. The potential gender difference is also of interest when considering, for example, the increasing research on overactive bladder symptoms in men with lower urinary tract symptoms, which are generally related with prostatic benign hyperplasia [26].

The correlation between the effect of treatment, measured as number of micturitions per day or

mean volume voided per micturition, was found in studies conducted for 4–6 or 10–12 wk. This is important in planning new trials and suggests that the effect of treatment on number of micturitions per day or mean volume voided per micturition is achieved through similar mechanisms. In this respect, a recent study reported that mean volume voided was the most sensitive overactive bladder parameter in clinical trials [27].

In conclusion, the results of this analysis suggest that in the evaluation of the efficacy of a drug for overactive bladder, the mean volume voided per micturition may be a useful measure of efficacy.

### Conflicts of interest

The material contained in the manuscript has not been published and has not been submitted for publication elsewhere and all authors have read and approved the manuscript.

The authors have no conflict of interest.

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