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Mattiasson, Anders; Blaakaer, J; Høye, K; Wein, A J

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Simplified bladder training augments the effectiveness of tolterodine in patients with an overactive bladder

A. MATTIASSON*, K. BLAAKAER†, A.J. WEIN‡ and the Tolterodine Scandinavian Study Group
Department of Urology, University Hospital, Lund, Sweden, *Department of Obstetrics and Gynaecology, Skejby Hospital, Aarhus, Denmark, †Helsetorget Legesenter, Elverum, Norway, and ‡Division of Urology, University of Pennsylvania Medical Center, Philadelphia, USA
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OBJECTIVES
To compare the efficacy of tolterodine plus simplified bladder training (BT) with tolterodine alone in patients with an overactive bladder.

PATIENTS AND METHODS
In a multicentre, single-blind study at 51 Scandinavian centres, 505 patients aged ≥18 years with symptoms of urinary frequency (≥8 micturitions/24 h) and urgency, with or without urge incontinence, were randomized to oral treatment with either tolterodine 2 mg twice daily plus simplified BT or tolterodine alone. Changes in voiding diary variables were evaluated after 2, 12 and 24 weeks of treatment. The patients’ perceptions of their bladder symptoms and tolerability (adverse events) were also determined.

RESULTS
In all, 501 patients (75% women) were evaluable on an intention-to-treat basis (244 on tolterodine+BT and 257 on tolterodine alone). Tolterodine significantly reduced the voiding frequency and increased the volume voided per void at all sample times; these effects were significantly increased by adding BT. At the end of the study the median percentage reduction in voiding frequency was greater with tolterodine+BT than with tolterodine alone (33% vs 25%, P<0.001), while the median percentage increase in volume voided per void was 31% with tolterodine+BT and 20% with tolterodine alone (P<0.001). There was a median of 81% fewer incontinence episodes than at baseline with tolterodine alone, which was not significantly different from that with tolterodine+BT (87%). The two groups had comparable median percentage reductions in urgency episodes. Some 76% of patients on tolterodine+BT reported an improvement in their bladder symptoms relative to baseline, compared with 71% on tolterodine alone. Tolterodine was well tolerated; the most common adverse event was dry mouth.

CONCLUSION
Tolterodine 2 mg twice daily is an effective and well tolerated treatment for an overactive bladder, the effectiveness of which can be augmented by a simplified BT regimen.

KEYWORDS
overactive bladder, tolterodine, bladder training

INTRODUCTION
Antimuscarinic agents such as tolterodine are an established first-line pharmacotherapy for the overactive bladder [1], a debilitating medical condition that impairs the lives of millions of people worldwide [2,3]. In clinical practice, such pharmacotherapy is often used in conjunction with behavioural techniques that aim to teach patients to modify abnormal voiding patterns, such as bladder training (BT) (‘retraining’) [4,5]. However, to date no prospective study has evaluated the efficacy of tolterodine pharmacotherapy combined with this form of behavioural intervention. Thus the objective of this study was to compare the efficacy of tolterodine 2 mg twice daily with simplified BT against tolterodine alone, in patients with an overactive bladder.

PATIENTS AND METHODS
This multicentre, randomized, single-blind, parallel-group study in patients with an overactive bladder was conducted at 51 Scandinavian centres (19 in Sweden, 18 in Norway and 14 in Denmark) between October 1999 and December 2000. The study was conducted in accordance with the latest revisions to the Declaration of Helsinki, the study protocol having received ethical approval from the Institutional Review Board/Ethical Committee of each participating centre. All patients gave written informed consent before the conduct of study procedures.

Men and women aged ≥18 years with symptoms of urinary frequency (≥8 micturitions/24 h on average) and urgency (a strong and sudden desire to urinate), with or without urge incontinence, as determined by voiding diaries completed during a 1-week run-in period, were eligible for inclusion. Patients were recruited on the basis of symptoms alone, with no recourse to urodynamic investigation. Women of childbearing potential were required to be using a reliable birth control method to enter the study. Exclusion criteria included: any contraindication to antimuscarinic therapy; use of electrostimulation therapy or BT within the previous 3 months; patients with an indwelling catheter or on intermittent catheterization; pregnancy and lactation; and use of anticholinergic agents or concomitant treatment for an overactive bladder (other than oestrogen replacement therapy started at least 2 months before study commencement).

After the 1-week run-in period, eligible patients were randomized (in balanced blocks of four, according to a computer-generated randomization list) to receive 24 weeks of treatment with either oral tolterodine 2 mg twice daily plus simplified BT, or tolterodine alone. The dosage of tolterodine could be reduced to 1 mg twice daily during the first 2 weeks, as an alternative to withdrawal, if adverse effects were intolerable. Patients in the BT group were provided with a written information sheet (see Appendix) that briefly outlined the principles of bladder retraining and explained simple techniques that could be used to help improve bladder control. The
Tolerance was evaluated in terms of adverse events reported throughout the 24-week treatment period and during 2 weeks of follow-up. All adverse events were recorded and categorized by intensity (mild, moderate, severe) and the likelihood of a causal relationship to study medication by the investigator. Compliance was monitored throughout the study by counting returned study medication; those patients who had taken ≥80% of the prescribed medication were considered compliant.

**STATISTICAL ANALYSIS**

The efficacy endpoints in this study were changes in voiding diary variables between baseline and weeks 2, 12, and 24, with particular focus on voiding frequency. Assuming a mean difference between the treatment groups of 0.7 voids/24 h and a common SD of 2.5, it was necessary to recruit 202 patients/group to achieve a significance level of 5% and 80% power. Allowing for withdrawals, the aim was to recruit 484 patients to be randomized equally to the two treatment groups. Efficacy was analysed for all randomized patients on an intention-to-treat basis, using the ‘last value carried forward’ approach. Between-group comparisons with respect to continuous variables were made using the nonparametric Wilcoxon rank-sum test because the data were not normally distributed. Continuous variables were summarized with medians, the 25th and 75th percentiles, and range. Categorical data are presented with counts and percentages and between-group comparisons were made using the Pearson chi-square test.

### RESULTS

In all, 505 patients were enrolled into the study, of whom four were withdrawn before receiving study medication (mainly because of withdrawal of consent). The intention-to-treat population therefore comprised 501 patients aged 19–86 years (median 63) who were predominantly women (75%). About half the patients had had their symptoms for at least 5 years before enrolment. In all, 15% of enrolled patients had received previous treatment for an overactive bladder. The two treatment groups were comparable in terms of baseline demographic and clinical characteristics, and no significant between-group differences were apparent (Table 1).

In each treatment group 90% of patients maintained their tolterodine dosage at 2 mg twice daily throughout the study. Overall, 391 patients (78%) completed 24 weeks of treatment, and completion rates were comparable for the two groups (tolterodine + BT, 77%; tolterodine alone, 80%).

### Table 1

The baseline demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment</th>
<th>Tolerodine + BT</th>
<th>Tolerodine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>244</td>
<td>257</td>
<td></td>
</tr>
<tr>
<td>Men/women (%)</td>
<td>177 (73)</td>
<td>67 (28)</td>
<td>201 (78)</td>
</tr>
<tr>
<td>Median (range):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age, years</td>
<td>62 (19–86)</td>
<td>63 (22–86)</td>
<td>75.5 (45–135)</td>
</tr>
<tr>
<td>body weight, kg</td>
<td>75.5 (45–135)</td>
<td>73 (45–125)*</td>
<td></td>
</tr>
<tr>
<td>No. (%) of patients with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>duration of symptoms</td>
<td>120 (49)</td>
<td>124 (48)</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>40 (16)</td>
<td>35 (14)</td>
<td></td>
</tr>
<tr>
<td>previous drug therapy for overactive bladder</td>
<td>26 (11.5)</td>
<td>30 (12)</td>
<td></td>
</tr>
<tr>
<td>previous surgery affecting lower urinary tract</td>
<td>143 (59)</td>
<td>165 (64)</td>
<td></td>
</tr>
<tr>
<td>Median (range):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no. of voids/24 h</td>
<td>10.3 (7.3–27.6)</td>
<td>10.6 (7.7–24.6)</td>
<td></td>
</tr>
<tr>
<td>no. of incontinence episodes/24 h</td>
<td>2.0 (0.3–20.3)</td>
<td>2.3 (0.3–16.3)</td>
<td></td>
</tr>
<tr>
<td>Volume voided/void, mL</td>
<td>156 (36–428)</td>
<td>153 (114–195)</td>
<td></td>
</tr>
<tr>
<td>No. of urgency episodes/24 h</td>
<td>6.0 (0–23.0)*</td>
<td>6.6 (0–34.3)</td>
<td></td>
</tr>
<tr>
<td>Adverse events, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>76 (31)</td>
<td>90 (35)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>15 (6)</td>
<td>21 (8)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (3)</td>
<td>14 (5)</td>
<td></td>
</tr>
<tr>
<td>Total no. with ≥ one adverse event</td>
<td>158 (65)</td>
<td>177 (69)</td>
<td></td>
</tr>
</tbody>
</table>

*Data missing for one patient; †For those patients reporting incontinence at baseline.
The main reasons for withdrawal were: adverse events (15%), lack of efficacy (3%), withdrawal of consent (2%), and protocol violations (1%). The two treatment groups were comparable in terms of the reasons for withdrawal, and 74% of patients in each treatment group were compliant in taking their medication throughout the study.

Voiding diaries provided for BT were collected from 95 randomly chosen patients in the BT group, 91 of which were evaluable for compliance. Diaries were considered to have been completed for a particular day if at least three voids were recorded. At 1 week (± 7 days), 65 patients had completed at least 1 day of the diary, with 57 having completed all 7 days. At 11 weeks (± 7 days), the corresponding numbers were 68 and 59. At 23 weeks, compliance had decreased, and 46 of the 56 patients having made a diary entry completed all 7 days.

**EFFECT ON VOIDING DIARY VARIABLES**

Compared with baseline there was a progressive and statistically significant decrease in voiding frequency in both treatment groups, with a maximum effect from week 12 onwards (Fig. 1). BT significantly increased the efficacy of tolterodine in reducing voiding frequency at all sample times (Fig. 1). Thus, at the end of the study the median percentage reduction for those patients receiving combined therapy was 33%, compared with a 25% reduction in voiding frequency for patients on tolterodine alone (Table 2). The augmenting of the effect of tolterodine on voiding frequency was paralleled by a significant improvement in the volume voided for those patients receiving BT, both groups achieving a highly significant increase in volume voided relative to baseline (Table 2). For the number of incontinence episodes, patients with this symptom had a median 81% reduction from baseline on tolterodine alone, which was not significantly different from that achieved with combined BT (87%; Table 2). The improvement in episodes of incontinence was accompanied by comparable reductions in episodes of urgency for both treatment groups.

**EFFECT ON PATIENT PERCEPTION OF BLADDER SYMPTOMS**

The two treatment groups were well balanced in terms of the baseline distribution of patients’ perceptions of problems caused by their bladder symptoms. Most patients reported that their symptoms caused at least some ‘moderate problems’ (tolterodine + BT, 92%; tolterodine alone, 93%). After 24 weeks of treatment there was an improvement in perception, with 66.5% of patients on tolterodine + BT now classifying their bladder problems as ‘minor’ or less, compared with 61.5% of those on tolterodine alone. No

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**FIG. 1.** The effect of 24 weeks of treatment with tolterodine 2 mg twice daily, with (green circles) or without BT (red squares), on: a, the number of voids/24 h; b, the number of incontinence episodes/24 h; c, the volume voided per void; and d, the number of urgency episodes/24 h, in patients with an overactive bladder. Values are medians. *P < 0.05, **P < 0.01 and ***P < 0.001 vs tolterodine alone.
significant between-group differences were apparent. Overall, 76% of those on tolterodine + BT achieved an improvement in their bladder symptoms relative to baseline, compared with 71% on tolterodine alone. Deterioration rates were 3% and 5%, respectively.

**TOLERABILITY**

All patients who received at least one dose of study medication were included in the tolerability analysis (244 on tolterodine + BT; 257 on tolterodine alone). Overall, treatment with tolterodine was well tolerated. However, 67% of patients experienced at least one adverse event during the study (about half of which were judged to be treatment-related) and the two treatment groups were comparable in this regard (Table 1). The profile of events was also similar between groups, in that dry mouth, headache and constipation were the most frequent adverse events (Table 1). The profile of events was also similar between groups, in that dry mouth, headache and constipation were the most frequent adverse events (Table 1). The profile of events was also similar between groups, in that dry mouth, headache and constipation were the most frequent adverse events (Table 1).

One patient died during this study, the result of an unrelated medical condition (aortic aneurysm). Few other serious adverse events were reported. In all, 20 patients (4%) reported a total of 25 serious adverse events, most of which resolved with no sequelae. Two events (chest pain and abdominal pain) that occurred in the same patient were considered drug-related.

**DISCUSSION**

Bladder training, which aims to teach patients to resist the sensation of urinary urgency and postpone voiding (thereby overcoming abnormal voiding patterns), is a recommended nonpharmacological option for treating an overactive bladder [6]. Numerous studies attest to the efficacy of this approach [7,8], but many clinics do not have sufficient time, funding or appropriately qualified staff to provide a BT service. The major limitation is the perception that BT requires the provision of a time-intensive patient education framework of written, visual and verbal instruction, with regular follow-up and reinforcement. There is also the known prerequisite for patients to be sufficiently motivated and mentally capable of participating in such training. Many physicians therefore resort to pharmacotherapy in the first instance, typically with an antimuscarinic agent such as tolterodine. Although such therapy is often used in combination with behavioural strategies, there is a paucity of data on the efficacy of this combined therapeutic approach [9]. The present study therefore aimed to address these issues, by examining whether a simplified BT programme (in the form of an instruction sheet, with no physician involved) would be acceptable to patients, and whether this approach would augment the known efficacy of tolterodine. To our knowledge, this study represents the largest clinical trial of combined therapy with BT and an antimuscarinic agent against pharmacotherapy alone.

Overall, the present findings confirm the favourable tolerability and therapeutic efficacy of tolterodine 2 mg twice daily in a large cohort of patients with an overactive bladder and representative of routine practice, and are in line with earlier studies [10–14]. After 24 weeks of treatment, patients

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**TABLE 2 Effect of 24 weeks of treatment with tolterodine 2 mg twice daily (T), either alone or with bladder training (BT), on voiding diary variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>P</th>
<th>T vs. baseline</th>
<th>T+BT vs. baseline</th>
<th>T+BT vs. T</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of voids/24 h at week 24</td>
<td>Tolterodine + BT</td>
<td>239</td>
<td>250</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of voids/24 h at week 24</td>
<td>Tolterodine</td>
<td>235</td>
<td>250</td>
<td>0.28</td>
<td>0.99</td>
</tr>
<tr>
<td>No. of evaluable patients</td>
<td>Tolterodine + BT</td>
<td>239</td>
<td>160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of evaluable patients</td>
<td>Tolterodine</td>
<td>235</td>
<td>160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) percentage change</td>
<td>Tolterodine + BT</td>
<td>−32 (−42.3, 21.3)</td>
<td>−25 (−38.8, −13.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (IQR) percentage change</td>
<td>Tolterodine</td>
<td>−32 (−42.3, 21.3)</td>
<td>−25 (−38.8, −13.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of urgency episodes/24 h at week 24</td>
<td>Tolterodine + BT</td>
<td>236</td>
<td>248</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of urgency episodes/24 h at week 24</td>
<td>Tolterodine</td>
<td>235</td>
<td>248</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>No. of evaluable patients</td>
<td>Tolterodine + BT</td>
<td>236</td>
<td>160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of evaluable patients</td>
<td>Tolterodine</td>
<td>235</td>
<td>160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) percentage change</td>
<td>Tolterodine + BT</td>
<td>−38 (−76.7, −14.1)</td>
<td>−38 (−68.7, −8.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (IQR) percentage change</td>
<td>Tolterodine</td>
<td>−38 (−76.7, −14.1)</td>
<td>−38 (−68.7, −8.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No. of incontinence episodes/24 h includes only those patients reporting incontinence at baseline. IQR, interquartile range.*
had a median 25% reduction in voiding frequency and those with leakage at baseline had a median 81% fewer incontinence episodes, changes that were paralleled by improvements in urgency and volume voided. Such benefits were apparent within 2 weeks of starting treatment, and reached a sustained plateau from week 12 onwards. When treatment was combined with simplified BT, the effectiveness of tolterodine on voiding frequency and volume voided was enhanced, although no further improvement in urgency or incontinence episodes was apparent. There were relatively few incontinence episodes at baseline among patients in this study (median 2.0 and 2.3 per day) so it is perhaps not unexpected that there was no additional effect of BT beyond the marked 81% median reduction achieved with tolterodine alone. Another possibility is that a significant proportion of the increased voiding frequency in patients with an overactive bladder is an adaptive coping mechanism, and therefore amenable to behavioural intervention in which patients focus on their voiding patterns. In contrast, urgency and subsequent incontinence is related to an underlying pathophysiological mechanism, so tolterodine is likely to have a greater effect on these variables.

It is often thought that an extensive personal interaction is required between the patient and a bladder control therapist to train and subsequently keep the patient motivated [8]. However, this study used a simplified approach in which patients were provided with voiding diaries and a simple set of written instructions on how to ‘retrain’ their bladders. As described above, this approach increased the efficacy of tolterodine and supports the view that a ‘minimalist’ approach to educating the patient about BT can be highly effective. That 77% of patients completed the study also suggests that the BT programme was well accepted by patients over the 24-week course of treatment. However, the indication that a third of patients assessed for compliance did not take the opportunity to use their training diaries may suggest that there is still room for improvement. It is possible that adding some type of limited interaction or reinforcement to the BT programme might further increase compliance and thus be more effective.

Despite the benefits of BT in the present study there are caveats, e.g. there is an acceptance that the patient has to be well motivated before BT and other behavioural interventions can be effective. Given that patients recruited to clinical trials tend to be more motivated than those in routine practice, patients included in this study may have been more willing to comply with the instructions relating to retraining their bladder. It must also be accepted that BT is not feasible in the cognitively impaired patient. Although there was no formal assessment of cognitive function in this study, only those patients able to read and follow written instructions, in the opinion of the investigator, were recruited. Patients who had cognitive impairment were thus unlikely to have been enrolled. However, despite such caveats, it is important to recognize that tolterodine per se achieved a favourable therapeutic outcome in patients with an overactive bladder, and therefore provides an effective therapy for those patients who cannot or will not comply with a BT programme.

While BT can be effective, one possible major limitation is that a decrease in patient motivation and subsequent adherence with the intervention over time may result in reduced longer-term efficacy. This is exemplified by the findings of Ferrie et al. [7], who reported an initial ‘success rate’ of 88% with BT that subsequently declined to 38% after 6 months. However, such a decline in efficacy was not apparent in the present study, the beneficial effect of combined tolterodine and BT being maintained for the full 24-week period. One explanation for this difference may be that the simplified BT regimen used in this study encouraged better patient adherence than the more traditional approach. A further possible explanation may be that concomitant tolterodine therapy itself augments the efficacy of BT, possibly because improved efficacy with combined treatment helps to maintain patient motivation and long-term adherence. However, while the long-term clinical efficacy of tolterodine alone has been clearly shown in previous trials [15,16], there are no studies to date that confirm whether the added benefit of combined treatment with tolterodine and BT seen in the present study can be extended beyond 6 months. In view of its unpredictability and the possibility of leaking a large volume of urine, urgency is a particularly distressing symptom for patients with an overactive bladder. However, to date the effect of antimuscarinic therapy on this symptom has not been studied in great detail. Previous studies have shown that tolterodine reduces the degree of urgency felt by patients, one study showing that the proportion of patients unable to hold urine at all upon feeling an urgent sensation to void was halved when given tolterodine therapy [14]. In the present study patients recorded all episodes of urgency, in some cases experiencing up to 34 daily episodes of urgency at baseline. In line with the findings of Chancellor et al. [14], tolterodine therapy reduced the daily number of episodes of urgency experienced by patients in this study, an effect that was not augmented by concomitant BT. Such findings add to the view that tolterodine therapy changes the nature of urinary urgency in patients with an overactive bladder.

In conclusion, the results of this study confirm that tolterodine 2 mg twice daily is an effective and well tolerated treatment for the overactive bladder, the effectiveness of which can be significantly augmented by a simplified BT regimen in patients willing and able to comply with such behavioural intervention.
ACKNOWLEDGEMENTS

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REFERENCES

7 Ferrie BG, Smith JS, Logan D.

Correspondence: Professor Anders Mattiasson, Department of Urology, University Hospital, 221 85 Lund, Sweden. e-mail: anders.mattiasson@urokir.lu.se

Abbreviations: BT, bladder training.

APPENDIX

A. TEXT SUPPLIED TO PATIENTS WHO RECEIVED TOLTERODINE PLUS SIMPLIFIED BT

Simplified bladder training programme

An overactive bladder is one that tends to contract on its own accord when you do not want it to. These uncontrolled contractions lead to feelings of urgency (a strong desire to void) and in some people can lead to urine leakage.

The tablets which we use to treat the overactive bladder are basically bladder sedatives. They selectively calm the bladder without having other calming effects on you. These tablets should decrease how often you feel the urge to urinate and may lessen the intensity of urgency that you experience. You can help the process by stretching your bladder. We know that overactive bladders become quieter if they are stretched. It is similar to blowing up a new balloon. At first it is stiff and difficult to inflate but when the inflation is repeated it gets easier.

You can stretch your bladder gradually and gently by reducing the number of times you urinate in a day. If you maintain the same fluid intake but reduce the number of times you urinate in a day, you will hold more in your bladder. If you hold more in your bladder, it will stretch.

The procedure for stretching your bladder involves delaying urination. When you get the feeling that you want to urinate, try and hold onto it for longer than you usually would. At first this may prove difficult, uncomfortable or at times painful. However, holding onto your urine will not harm you. You may find it easier to practice this at times when you feel safe, such as when you are at home. On those occasions, really try and push it. Try to achieve a good bladder stretch. Gradually, you should find that you can delay, with growing confidence, for longer periods of time. Your target is to reduce your urination frequency to around 5–6 times in 24 h.

One technique to use when you feel a desire to urinate is to concentrate on a task which you need to complete such as making a grocery list, balancing a check book, or some other task that requires a great deal of concentration. Another technique is to sit and take a number of deep breaths, concentrating on the breathing and not the bladder sensation. Often, the desire to urinate will pass using these techniques. If you wake at night with a desire to urinate, do so. If you don’t it will only keep you awake.

An important part of stretching your bladder is to keep track of your progress. Therefore, you should consider completing a urination chart every other week. This is very important and will allow you to see the progress you make.

Two final items: it is very important to take the tablets consistently as prescribed, and it is very important to maintain your normal fluid intake. Do not decrease (or increase) your normal fluid intake during the study.

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B. TEXT SUPPLIED TO PATIENTS WHO RECEIVED TOLTERODINE THERAPY ALONE

General instructions

An overactive bladder is one that tends to contract on its own accord when you do not want it to. These uncontrolled contractions lead to feelings of urgency (a strong desire to
void) and in some people can lead to urine leakage.

The tablets which we use to treat the overactive bladder are basically bladder sedatives. They selectively calm the bladder without having other calming effects on you. These tablets should decrease how often you feel the urge to urinate and may lessen the intensity of urgency that you experience.

It is very important to take the tablets consistently as prescribed. It is also important that you maintain your normal fluid intake. Do not decrease (or increase) your normal fluid intake during the study.

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