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ORIGINAL RESEARCH

What Are Realistic Expectations to Become Free of Overactive Bladder Symptoms? Experience from Non-interventional Studies with Propiverine

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ABSTRACT

Introduction: Unmet expectations are a major cause of perceived treatment failure and discontinuation of treatment. To enable evidence-based counselling of patients on realistic expectations, we determined the chance of patients with overactive bladder becoming free of a given symptom upon treatment with a muscarinic antagonist in a non-interventional setting.

Methods: Two non-interventional studies included 1335 and 745 patients, respectively, who received 30 or 45 mg q.d. propiverine ER for 12 weeks. They were monitored for becoming free of urgency, urinary incontinence, frequency, or nocturia. Analyses were also performed in subgroups defined by basal symptom severity, age, and gender. Categorical data are shown as a percentage of the respective population. Continuous data are expressed as means or as median depending on whether the variability was considered to exhibit a normal distribution.

Results: The probability of becoming symptom-free was largest for incontinence and frequency (about 50%), but lesser for urgency (about 20%) and nocturia (about 10%). Greater basal severity of a symptom reduced the chance to become free of that symptom upon treatment, but the chance to become free of incontinence and frequency was still considerable. Age and gender had only minor if any effects on the chance of becoming symptom-free. These findings are in line with those of a limited number of randomized controlled trials.

Conclusion: These data provide an evidence base for the counselling of patients with overactive bladder on realistic expectations of treatment outcomes. We propose that realistic expectations can lead to greater long-term adherence.

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PLAIN LANGUAGE SUMMARY

Unmet expectations are a major reason why patients with overactive bladder syndrome discontinue treatment. To enable evidence-based counselling of patients on realistic expectations, we have determined the chance that patients with overactive bladder become free of urgency, incontinence, voiding frequency, and nocturia. Two non-interventional studies included 1335 and 745 patients, respectively, who received 30 or 45 mg q.d. propiverine ER for 12 weeks. Analyses were also performed in subgroups defined by basal symptom severity, age, and gender. The probability of becoming symptom-free was largest for incontinence and voiding frequency (about 50%), but lesser for urgency and nocturia (about 20%). Greater basal severity of a symptom reduced the chance to become free of that symptom upon treatment, but the chance to become free of incontinence and frequency was still considerable. Age and gender had only minor if any effects on the chance of becoming symptom-free. These data provide an evidence base for the counselling of patients with overactive bladder on realistic expectations of treatment outcomes. We propose that realistic expectations can lead to greater long-term adherence.

Keywords: Overactive bladder syndrome; Patient counselling; Propiverine; Success rate; Treatment

Key Summary Points

Why carry out this study?

Unmet expectations are a key reason for poor long-term adherence to medical treatment in overactive bladder syndrome.

Evidence-based counselling on realistic treatment expectations requires data on probability of reaching patient-relevant outcomes, i.e., becoming free of a given symptom.

What did the study ask?

Data from two non-interventional studies were analyzed to determine the probability of becoming free of urgency, incontinence, frequency, and nocturia.

What were the study outcomes/conclusions?

Chances of becoming symptom-free are highest for incontinence and frequency, lower for urgency and nocturia, and lowest for becoming free of all overactive bladder symptoms.

What was learned from the study?

Real-world data are provided to enable evidence-based counselling of patients on realistic expectations in overactive bladder syndrome.

INTRODUCTION

Muscarinic antagonists are a cornerstone in the medical treatment of patients with overactive bladder syndrome (OAB) [1, 2]. They provide symptom relief but not cure of the condition, necessitating long-term treatment. Nonetheless, long-term adherence to treatment with muscarinic antagonists is poor [3–5]. Key reasons for this include issues of tolerability and efficacy, but unrealistic patient expectations also appear to play a major role for premature discontinuation [3, 5, 6] and for primary unresponsiveness in OAB treatment [7]. This necessitates counselling patients with OAB on realistic expectations on the treatment outcomes to improve adherence and, thereby, long-term efficacy.

Evidence-based counselling must rely on data. Typically reported findings from randomized controlled trials (RCT) include mean or median reduction in each symptom, very often reported as baseline-adjusted improvements. Explaining such numbers to patients can be challenging, particularly when aspects of study design such as randomization, blinding, and single-blind run-in periods are to be discussed. More important to most patients is how likely

they will get rid of a symptom. The most bothering symptom can differ between patients. Only a small fraction of RCT reports on the percentage of patients becoming free of a symptom. For instance, a recent systematic review and network meta-analysis identified only 11 RCT using muscarinic receptor antagonists, two trials with mirabegron, and one with onabotulinum toxin that reported on becoming continent upon treatment and expressed these findings as the odds ratio relative to placebo or to onabotulinum toxin [8]. Our own searches identified a small number of later RCT reporting dry rates upon treatment with a muscarinic receptor antagonist [9–12], a β_3-adrenoceptor agonist [13], or a muscarinic antagonist/β_3-adrenoceptor agonist combination [9]. However, epidemiological studies indicate that patients with incontinence represent only approximately one-third of the overall OAB population [14].

Notably, even fewer RCT report on becoming free of symptoms other than incontinence. Thus, we identified only two RCT reporting on becoming free of urgency and/or frequency upon treatment with a muscarinic antagonist or placebo [12, 15], one reporting on becoming free of urgency, daytime frequency, and nocturia and total micturition frequency and concomitantly of urgency, daytime frequency, and incontinence (pooled secondary analysis of six previously reported RCT) [10]; one very small RCT (fewer than 30 patients per arm) reported on becoming free of frequency upon treatment with cizolirtine, an inhibitor of substance P and calcitonin gene-related peptide release [16]. Thus, the total evidence base on the probability of becoming free from symptoms other than incontinence is very limited.

Another problem with evidenced-based counselling of patients on the chance of becoming free of the most bothersome symptom is that all of the aforementioned data come from RCT. While RCT have high internal validity, their external validity is low because of their typically long list of inclusion and exclusion criteria, very often the use of a single-blind run-in period during which symptom improvement most likely has already occurred to some extent, and the knowledge of participating patients to be part of a study. In contrast, non-interventional studies (NIS) are not suitable to demonstrate the efficacy of a treatment relative to placebo, i.e., they have low internal validity; however, they have high external validity because of reflecting the patient population receiving treatment under real-world conditions. Studies in related indications such as male lower urinary tract symptoms (LUTS) found that improvements of symptoms upon treatment with an α_1-adrenoceptor antagonist were greater in NIS than in RCT [17, 18]. Similarly, the indirect comparison between one RCT [19] and one NIS [20] with tolterodine for the treatment of OAB indicated a considerably larger fraction becoming continent in the NIS than in the RCT (59% vs. 26%). Thus, NIS possibly have greater value for evidence-based patient counselling on realistic treatment expectations, but this assumption has not been tested thoroughly. Against this background, our aim was to explore the probability of becoming free of urgency, incontinence, frequency, and nocturia upon medical treatment on the basis of data from two large NIS using the muscarinic antagonist propiverine. These analyses were also done in subgroups stratified by baseline severity of symptoms, age, and gender.

METHODS

Study Design

Our analyses are based on a post hoc analysis of two previously reported NIS of similar design [21, 22]. Each study had been approved by the responsible ethical committee (Sächsische Landesärztekammer EK-BR-14/12-1 and EK-BR-18/14-1). The underlying studies had been performed in accordance with the Helsinki Declaration of 1964, and its later amendments. Consent to participate is not applicable for a NIS in which only pseudonymized information was provided to the investigators. Study I included 1335 patients and was considered exploratory. Study II included 745 patients and was used to explore the robustness of findings from study I. For each study, participating

physicians were requested to systematically document findings on patients receiving propiverine ER (30 or 45 mg q.d.) on the basis of physician judgement during a 12-week observation period. In accordance with the non-interventional character of the studies, no inclusion or exclusion characteristics were specified other than those defined in the applicable standard prescribing information. Moreover, the protocol did not specify whether OAB-related data were collected from voiding diaries or from patient recollection, but the applicable German guideline recommended voiding diaries [23]. More information on study design, demographics, patient flow, and discussions of the relative strengths and weaknesses of this non-interventional approach is provided in the primary publication [21].

Data Analysis

Patients were included in the present analysis if they had a recorded value for a parameter at baseline and after 12 weeks of treatment; patients not exhibiting a symptom at baseline (no urgency, incontinence or nocturia, or frequency less than 8 per 24 h) were excluded from the analysis of that symptom but not the overall analysis. The average median of both studies was used to define subgroups based on baseline severity or age. While we report on a post hoc analysis, all analyses were prespecified prior to calculation of becoming symptom-free defined as zero episodes for urgency, incontinence, and nocturia and as seven or fewer for micturitions. There were two exceptions: Firstly, nocturia data were reanalyzed defining lack of symptoms as at most one episode. Secondly, we analyzed the data after 12 weeks to identify patients being free of all four symptoms ("totally symptom-free").

Categorical data (patients becoming symptom-free) are shown as a percentage of the respective population. Continuous data are expressed as means (age, height, weight, body mass index (BMI)) or as median (OAB duration and daily episodes of urgency, incontinence, voids, and nocturia) [22]. Patients with medically implausible values (urgency > 50,

Table 1 Subjects with data for a given symptom at baseline, subjects exhibiting that symptom, symptom severity at baseline, and subjects with data after 12 weeks

Symptom	Subjects with data at baseline	Subjects having a symptom at baseline	Median episode number at baseline	Subjects with data after 12 weeks
Study I				
Urgency	1151	1134	10	1004
Incontinence	1149	785	4	681
Frequency	1305	1253	13	1139
Nocturia	1318	1269	3	1154
Study II				
Urgency	638	621	10	550
Incontinence	589	418	5	365
Frequency	729	683	13	630
Nocturia	730	706	3	648

Note that the nocturia data are based on the definition of at least one episode as presence of symptoms and zero episodes as absence of symptom. When presence was defined as at least two episodes and absence as at most one episode, 1065 and 594 patients exhibited nocturia at baseline in studies I and II, respectively, with a median of three episodes in both studies

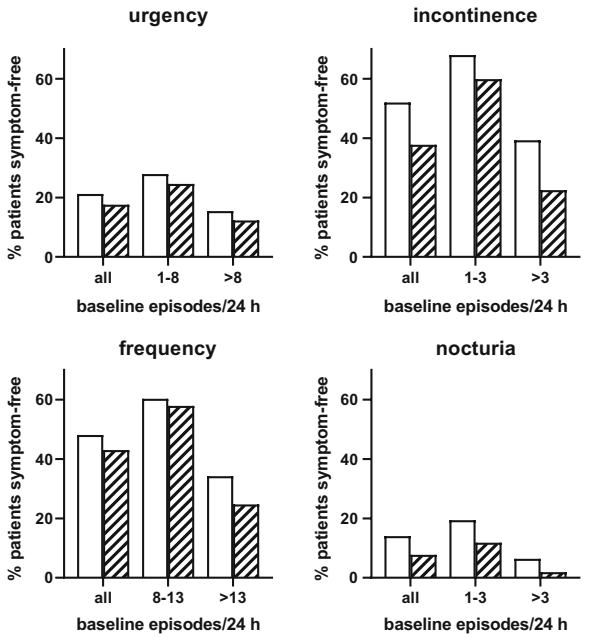

Fig. 1 Change in voiding diary parameters in total groups and subgroups based on baseline symptom severity in studies I (clear bars) and II (hatched bars). Data in the "all" group are identical to those shown in Figs. 2 and 3. Being free of nocturia was defined as zero episodes for these analyses

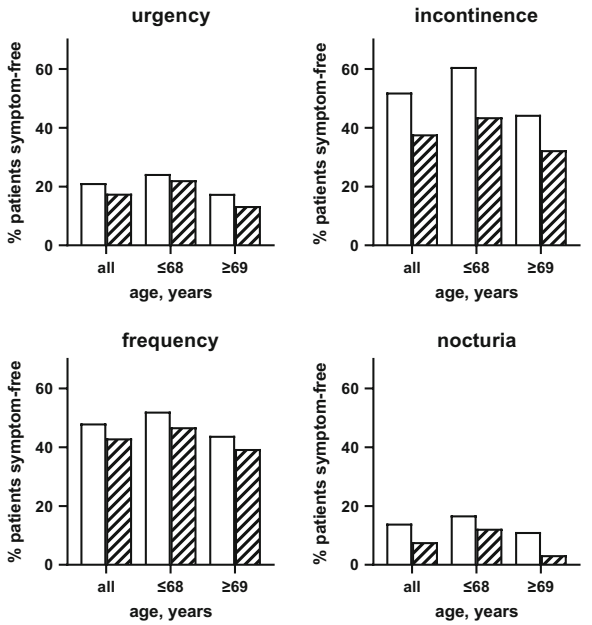

Fig. 2 Change in voiding diary parameters in total groups and subgroups based on age in studies I (clear bars) and II (hatched bars). Data in the "all" group are identical to those shown in Figs. 1 and 3. Being free of nocturia was defined as zero episodes for these analyses

incontinence > 30, frequency > 40, and nocturia > 20 episodes/24 h) were excluded from the analysis for that symptom and visit; this affected four patients each for urgency and frequency, one each for incontinence and nocturia in study I and none in study II. One patient in study II reported to be 1 year old was also excluded because of lack of plausibility. Table 1 reports the numbers of subjects with data at baseline and after 12 weeks of treatment in each study.

On the basis of the exploratory character of our analyses and in line with recent recommendations from leading statisticians [24, 25], we did not apply hypothesis-testing statistical tests to our exploratory analysis of the two data sets. Rather we looked whether group differences shown in Figs. 1, 2, and 3 were of likely medical relevance and whether they were consistent across the two studies.

RESULTS

Overall Group

Baseline symptoms and median improvements in the overall cohort of each study have been reported previously [21]. We now found in both studies that about 50% of all patients became free of incontinence and frequency, whereas only about 20% became free of urgency (Fig. 1). Only about 10% became free of nocturia (Fig. 1). When absence of nocturia was defined as at most one nocturnal void (i.e., lack of clinically relevant nocturia; post hoc analysis), 611 (57.4%) and 283 (47.6%) patients in studies I and II, respectively, became free of nocturia.

The status of totally symptom-free (post hoc analysis; not allowing any nocturia episodes) was reached by 94 (7.8%) and 33 (4.9%) patients in studies I and II, respectively. When considering at most one nocturia episode as symptom-

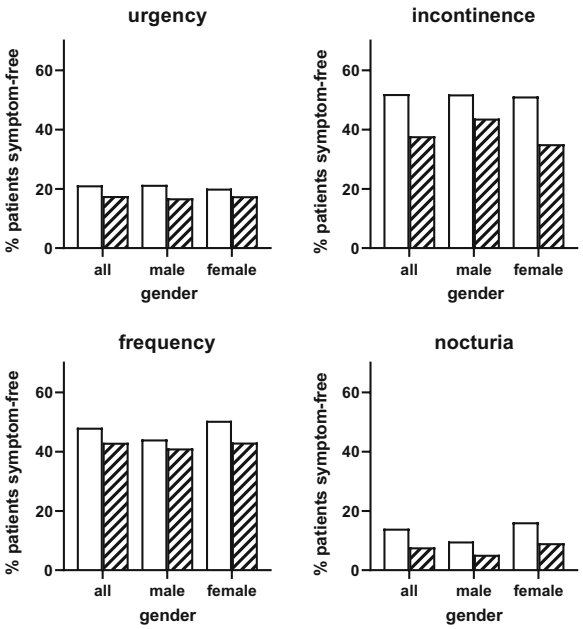

Fig. 3 Change in voiding diary parameters in total groups and subgroups based on gender in studies I (clear bars) and II (hatched bars). Data in the "all" group are identical to those shown in Figs. 1 and 2. Being free of nocturia was defined as zero episodes for these analyses

free, a totally symptom-free status was achieved by 220 (18.2%) and 105 (15.5%) patients in studies I and II, respectively.

Subgroup Analyses

Table 2 shows baseline data in each subgroup. Patients with greater symptom severity at baseline less often became symptom-free (Fig. 1). However, even among those with greater baseline severity, 15.4% and 12.3% became free of urgency in studies I and II, respectively, 39.3% and 22.5% free of incontinence, 34.2% and 24.7% free of frequency, and 6.4% and 1.9% free of nocturia.

Older subjects (at least 69 years of age) were somewhat less likely to become symptom-free (Fig. 2). However, even in the older subgroups of both studies 17.5% and 13.4% became free of urgency, 44.4% and 32.4% free of incontinence, 43.9% and 39.4% free of frequency, and 11.2% and 3.3% free of nocturia.

Male and female patients similarly often became free of urgency (Fig. 3). Men slightly more often became dry than women in study II (with a negligible difference in study I), whereas women slightly more often became free of frequency (mainly study I) and nocturia in both studies (Fig. 3).

DISCUSSION

Critique of Methods

Prior to discussing our data, we would like to draw attention to specific aspects of data acquisition and analysis. In line with the expectation of many patients, we applied the most stringent definition of treatment success, i.e., becoming free of a given symptom. As urgency, nocturia, and incontinence are pathological phenomena, we defined symptom-free as a reported absence of these symptoms. While nocturia defined as at least two nocturnal voids per night is associated with a markedly reduced quality of life and healthcare-seeking behavior [26, 27], experiencing up to one nocturnal void per night typically is not [28]. Therefore, we made a post hoc decision to also explore becoming symptom-free of nocturia if this is defined as at most one nocturnal void. On the basis of epidemiological studies [29, 30] and in line with typically applied definitions in RCTs [10, 11, 16], we operationally defined lack of frequency as at most seven micturitions.

All analyses are based on subjects who had data on a given symptom as defined above both at baseline and after 12 weeks of treatment. Therefore, reported percentages of becoming symptom-free do not account for those prematurely discontinuing treatment. As these rates had been low in the underlying studies [21], we do not expect this to have a major impact on our conclusions. Moreover, our outcome assessments are consistent with the limited data on becoming symptom-free in RCT with propiverine that had been analyzed on an intention-to-treat basis (see below).

While representing a post hoc analysis of previously reported NIS [21], the present analysis protocol had been finalized before data

Table 2 Characteristics (subjects in group and median severity and median age at baseline) of patients with smaller and greater baseline severity, younger and older age, and male and female patients in studies I and II

Symptoms	Less severe at baseline		More severe at baseline	
	Subjects at baseline	Median episodes at baseline	Subjects at baseline	Median episodes at baseline
Study I				
Urgency	433	5.5	571	13
Incontinence	294	2	387	6
Frequency	604	11	535	16
Nocturia	667	3	487	4
Study II				
Urgency	232	6	317	12
Incontinence	147	2	218	6.5
Frequency	347	11	283	16
Nocturia	382	3	266	4

	Younger		Older	
	Subjects at baseline	Median age at baseline	Subjects at baseline	Median age at baseline
Study I				
Urgency	494	58	504	75
Incontinence	321	59	356	75
Frequency	585	58	545	75
Nocturia	576	58	572	75
Study II				
Urgency	270	59	276	75
Incontinence	172	61	188	74
Frequency	316	59	310	75
Nocturia	316	59	330	75

	Male		Female	
	Subjects at baseline	Median episodes at baseline	Subjects at baseline	Median episodes at baseline
Study I				
Urgency	351	10	617	10
Incontinence	202	4	457	4
Frequency	383	13	724	13
Nocturia	392	3	727	3

Table 2 continued

	Male		Female	
	Subjects at baseline	**Median episodes at baseline**	**Subjects at baseline**	**Median episodes at baseline**
Study II				
Urgency	202	9.5	320	10
Incontinence	103	3	242	5
Frequency	224	13	371	13
Nocturia	231	3	383	3

Groups were defined by having at most eight or at least nine urgency episodes, at most three or at least four incontinence episodes, at most 13 or at least 14 voids, and at most three and at least four nocturia episodes, and younger as at most 68 years of age and older as at least 69 years of age

were inspected relative to the parameters of interest, except for the explicitly indicated post hoc analyses. Because our analyses are explorative, we did not apply hypothesis-testing statistical analysis. However, we have done all analyses in parallel for two studies of similar design to increase the robustness of our findings. While the results of the two studies exhibited some quantitative differences, the overall outcomes were comparable.

The present analyses are based on NIS and cannot be used to define efficacy; such proof had been obtained in many RCT including comparisons to placebo [11, 15, 31, 32] or to other muscarinic antagonists [15, 32–34]. While RCT have strict inclusion and exclusion criteria and standardized symptom assessment, they can be of limited value for the counselling of patients because participants in RCT represent a selected population and participating patients and physicians find themselves in an artificial setting; moreover, they typically include a single-blind run-in period during which some alterations of symptoms possibly have occurred. In contrast, NIS lack standardized symptom assessment and strict inclusion and exclusion criteria other than those in the prescribing information but provide information on outcomes in a real-world urological office. While subjective assessments by patients (which may have occurred in some patients in our NIS) may overestimate some OAB symptoms [35], patient satisfaction, and by inference treatment adherence, depends on subjective assessment. This assumption is validated by the observation that rates of becoming symptom-free in the present NIS are comparable to those in two previously reported RCT with propiverine and other muscarinic antagonists (see below). Therefore, we propose that NIS have less internal validity than RCT, but their findings are more applicable for the counselling on expected treatment outcomes. The representativeness of the present cohorts for real-world evidence is supported by the fact that the observed efficacy based on mean/median changes was comparable to that in two previous NIS with propiverine [36, 37].

Probability of Becoming Symptom-Free

Our data extend and confirm findings on becoming symptom-free that have been reported in a limited number of RCT for incontinence and an even smaller number for other OAB symptoms. A limited number of studies in patients with OAB have reported on becoming free of incontinence [8–12, 16]; the dry rate with placebo or a muscarinic antagonist was 30–38% and 26–69%, respectively. Other than general considerations on differences between RCT and NIS (see above), an indirect comparison between an RCT [19] and a NIS [20] testing tolterodine had indicated that the chance of

becoming free of incontinence was considerably greater in the NIS than in the RCT (59% vs. 26%). Reported dry rates in the present two NIS with propiverine were in the range of previously reported RCT, including those with propiverine [11, 12, 15], or the tolterodine NIS. This difference with tolterodine may be attributable to the fact that the tolterodine RCT reported the lowest dry rate among all muscarinic antagonist RCT, whereas the tolterodine NIS had a slightly higher dry rate than the two with propiverine. Against our pre-study assumptions, these data do not support the idea that NIS report systematically higher dry rates than RCT. Rather they suggest that the overall chance of an incontinent patient with OAB becoming dry is about 50% and is greater than with placebo treatment [8]. Looking at all studies reporting dry rates, we see no compelling evidence that it differs in a clinically meaningful way between the various muscarinic antagonists. This is line with the general observations that mean or median reductions in OAB symptoms are comparable for all muscarinic antagonists [38].

To the best of our knowledge, only four reports from RCT [10, 12, 15, 16] (one of them based on fewer than 30 patients per arm) and one NIS [20] are available for becoming free of OAB symptoms other than incontinence. Although urgency is the defining symptom of OAB [39], only very few studies reported on becoming free of urgency after treatment. The percentage of patients becoming free of urgency after treatment with placebo, fesoterodine, propiverine, solifenacin, or tolterodine was 14–21%, 24%, 31%, 33–37%, and 42%, respectively. The about 20% of urgency-free subjects in the present two NIS are comparable to the fesoterodine data. The observation that the chance of becoming free of urgency is smaller than that of incontinence had also been made within each study. Only few studies with muscarinic antagonists have provided data for frequency [10, 15], indicating a chance of 21–41%, 42–54%, 26%, and 29–37% for placebo, fesoterodine, propiverine, and solifenacin, respectively; the present estimates from NIS with propiverine (43–48%) fall within that range. Of note, the normalization rate for urgency and frequency exceeded that observed with placebo within each RCT. Only one study has reported data for nocturia and found a 30% chance with placebo and 32–33% chance with fesoterodine [10]; the two NIS with propiverine found 8–14% when the strict definition was applied, but 48–54% when up to one nocturia episode was allowed. Some patients may ask about the chance to become totally free of OAB symptoms. This probability was reported to be less than 10% with placebo or fesoterodine in RCT [10] or in the present two NIS with propiverine. When the looser definition of being free of clinically relevant nocturia was applied, this increased to 16–18% in the present NIS. Taken together, these findings indicate that the chance of becoming symptom-free is higher for incontinence and frequency, lower for urgency and nocturia, and lowest for totally becoming symptom-free. A low chance of becoming free of nocturia upon treatment with a muscarinic antagonist is in line with the general observation that this drug class, like α_1-adrenoceptor antagonists or 5α-reductase inhibitors, has little effect relative to placebo to reduce the number of nocturia episodes [40]. The more limited data for symptoms other than incontinence also do not support the idea that NIS detect more patients becoming free of an OAB symptom than RCT.

While the above data are suitable for the evidence-based counselling of patients with OAB prior to initiation of treatment, patients differ in their baseline symptom severity, age, or gender. Findings from a NIS with tolterodine indicated that baseline intensity of a given symptom was strongly associated with the chance of becoming symptom-free upon treatment with odds ratios of about 0.75 for incontinence and frequency and 0.85 for urgency [20]. The present data confirm that greater baseline severity of a symptom is associated with a reduced chance to become free of that symptom upon treatment. Moreover we found it remarkable that even among subjects with more severe incontinence or frequency at baseline, the probability of becoming symptom-free upon treatment was still about 30%.

Previous work had identified that older age also is associated with a smaller chance to become symptom-free (odds ratio of about 0.98

for each year of age) [20]; RCT with fesoterodine also suggested that greater age is associated with a somewhat smaller chance to become symptom-free [10]. In the present NIS, older subjects had a somewhat reduced probability of becoming symptom-free, but that chance was still greater than 40% in those aged 69 years or more.

NIS with muscarinic antagonists have typically reported that symptom improvement at the group level is comparable in both genders, for instance with darifenacin [41] or solifenacin [42]. In contrast, previous NIS data with tolterodine indicated that male gender was associated with an odds ratio of about 0.75 for becoming free of urgency and frequency, but 1.45 for becoming free of incontinence [20]. In the present NIS, gender was not associated with a major difference in becoming symptom-free.

CONCLUSIONS

Our data provide a basis for the evidence-based counselling of patients with OAB on the probability of becoming symptom-free with treatment. The data suggest that the chance is largest for incontinence and frequency (about 40–50%) and lower for urgency and nocturia (about 10–30%), whereas the chance to become free of all symptoms is less than 10% unless a looser definition of nocturia-free is applied. While patients with greater baseline values have a smaller chance to become symptom-free, age and gender have only limited effects. The data do not support the idea that NIS overestimate success rates relative to RCT or that major differences in efficacy exist between muscarinic antagonists. A critical limitation of these findings is that they are largely based on studies with a 12-week duration. However, both RCT [43] and NIS [44] suggest that the efficacy of muscarinic antagonists is stable for at least 9–-12 months if patients stay on treatment. These data should enable evidence-based counselling of patients on realistic treatment expectations. We hope that such counselling will improve patient adherence and, thereby, long-term outcomes in patients with OAB.

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Author Contributions. Conceptualization: SM, MCM. Methodology: AEM, MO, TS, SM, JdlR, MCM. Formal analysis and investigation: AEM. Writing—original draft preparation: AEM, MCM. Writing—review and editing: MO, TS, SM, JdlR. Funding acquisition: not applicable. Supervision: MCM.

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Compliance with Ethics Guidelines. Both studies had been approved by the responsible ethical committee (Sächsische Landesärztekammer EK-BR-14/12-1 and EK-BR-18/14-1). The underlying studies had been performed in accordance with the Helsinki Declaration of 1964, and its later amendments. Consent to participate is not applicable for a

non-interventional study in which only pseudonymized information was provided to the investigators.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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