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## Do gender, age or life style factors affect responses to anti-muscarinic treatment in overactive bladder patients?

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**Do gender, age or life style factors affect responses to anti-muscarinic treatment in overactive bladder patients?**

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3 Do gender, age or life style factors affect responses to anti-muscarinic treatment in overactive  
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5 bladder patients?  
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53 Author contributions  
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55 All authors jointly developed the idea for the analyses underlying the present manuscript. The  
56  
57 data had been collected by 1155 German physicians and were analyzed by a contract research  
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3 organization based upon a statistical analysis plan jointly developed by all authors. The  
4  
5 manuscript was drafted by Tim Schneider and Martin C. Michel and critically revised for  
6  
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27 from Allergan, Astellas, Bayer, Lilly and Pfizer.  
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3 ABSTRACT  
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8 Aims: Gender, age, obesity, smoking, and alcohol or caffeine intake have been shown or  
9 proposed to be risk factors for the prevalence and/or severity of the overactive bladder  
10 symptom complex (OAB) or related parameters. We have explored whether any of these  
11 factors affects the therapeutic response to a muscarinic receptor antagonist during routine  
12 clinical use.  
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22 Methods: Data were analyzed from 3766 OAB patients (77.1% female, age  $62.6 \pm 12.8$  years)  
23 participating in an observational, open-label post-marketing surveillance study of the safety  
24 and efficacy of darifenacin. Multiple logistic regression models were applied to explore the  
25 effect of potential OAB risk factors on the darifenacin treatment-associated improvement of  
26 OAB symptoms, patient's subjective rating of bladder problems, and global efficacy and  
27 tolerability.  
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39 Results: Age and (less consistently) gender were statistically significantly correlated with  
40 efficacy parameters, but the extent of their impact was judged to be too small to be clinically  
41 relevant. Except for a very small effect of body mass index on urgency episode improvement,  
42 none of the life style-associated factors had significant effects on the efficacy of darifenacin.  
43 Except for a very small age effect, none of the potential risk factors had significant effects on  
44 global tolerability.  
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55 Discussion and conclusions: We conclude that the efficacy and tolerability of a muscarinic  
56 receptor antagonist such as darifenacin is largely independent of potential OAB risk factors  
57 such as gender, age, obesity, smoking and alcohol or caffeine intake.  
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6 Key words: overactive bladder, urinary incontinence, gender, age, obesity, smoking, alcohol,  
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8 caffeine, darifenacin  
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12 What is already known about this topic?  
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14  
15 Gender, age, obesity, smoking, and alcohol or caffeine intake have been shown or proposed to  
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17 be risk factors for the prevalence and/or severity of the overactive bladder symptom complex  
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19 (OAB) or related parameters but their possible effect on treatment outcomes is unknown.  
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24 What does this article add?  
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27 Gender, age, obesity, smoking, and alcohol or caffeine intake apparently have little effect on  
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29 the results of OAB treatment with a muscarinic antagonist.  
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## INTRODUCTION

The overactive bladder symptom complex (OAB) is defined by the presence of urgency, with or without incontinence, frequently accompanied by urinary frequency and nocturia (1). It is a very common condition in the general adult population (2-4) with major adverse effects on quality of life of the afflicted patients and considerable costs to society. While the causes of OAB and specifically urgency remain largely unclear (5), a number of risk factors have been demonstrated or proposed. A major risk factor is ageing, as the prevalence of OAB consistently increases with age (2-4, 6). While gender does not appear to be a risk factor for the presence of OAB in population-based studies (2-4), the vast majority of patients receiving OAB treatment are women (7, 8).

Additionally, a number of life-style factors have been proposed to be risk factors for OAB. Earlier studies have reported obesity, typically assessed as a high body mass index (BMI), (9-12) or smoking (10, 11) to be risk factors for incontinence in general but did not differentiate between stress and urgency incontinence. While obesity and smoking (via the associated frequent coughing) are pathophysiologically plausible risk factors for stress incontinence, their link to OAB or urgency incontinence is less clear. Nevertheless, both obesity and, to a lesser extent, smoking have also been linked as risk factors to urgency incontinence (13), detrusor instability (14) and the classical albeit non-specific OAB symptom nocturia (15) although such associations have not been confirmed for both factors in all studies (15, 16). An increased intake of alcohol and/or caffeine may affect voiding patterns based upon the diuretic effects of these agents. While increased intake of alcohol and/or caffeine have been proposed as risk factors for OAB or detrusor instability, the existing data are equivocal (14-17). The life style-associated factors are of particular interest as they are modifiable, i.e. theoretically offer

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3 the possibility to improve the condition (18). For example, a recent randomized trial has  
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5 demonstrated that alterations of fluid intake can affect symptoms in OAB patients (19)  
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8 whereas weight loss may improve incontinence in obese patients (20).  
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12 Muscarinic receptor antagonists are the main treatment option for OAB patients (21, 22).

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14 While they have consistently been shown to be superior to placebo, it remains unclear how  
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16 potential risk factors for OAB may affect the treatment response to these drugs. For example,  
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18 age may alter the expression of muscarinic receptors in the bladder and its responsiveness to  
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20 muscarinic receptor ligands (23), but some clinical data indicate that age may have limited  
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22 effect on treatment responses (7, 24). Whether modifiable factors such as obesity, smoking or  
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24 alcohol and caffeine ingestion may affect the therapeutic response to muscarinic antagonists  
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27 has not been investigated to our knowledge.  
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34 Darifenacin is a muscarinic receptor antagonist with efficacy in the treatment of OAB  
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36 symptoms in several randomized, double-blind, placebo-controlled studies (25-27). Against  
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38 the above background, we have used the database from a recent large observational study of  
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40 the safety and efficacy of darifenacin to explore possible roles of gender, age and life-style  
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42 factors in the clinical response to a muscarinic receptor antagonist.  
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## 48 MATERIAL AND METHODS

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53 This manuscript describes a post-hoc analysis of a large, open-label, observational study into  
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55 the safety and efficacy of darifenacin which had been performed as part of its post-marketing  
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57 surveillance in Germany. Thus, no specific inclusion and exclusion criteria were applied other  
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59 than a minimum age of 18 years and the recommendations from the Summary of Product  
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3 Characteristics for darifenacin. The participating 1155 physicians (including 81.0% board-  
4 certified and office-based urologists, 13.8% general practitioners) were asked to  
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6 systematically record their observation of patients receiving darifenacin based upon their  
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8 medical judgment. Based upon the package insert, recommended darifenacin doses were 7.5  
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10 and 15 mg q.d. The planned observation time was 12 weeks. At the time the study was  
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12 performed, ethical committee approval, registration in clinical trials databases or written  
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14 patient consent were neither required nor recommended for purely observational studies, such  
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16 as this one, in Germany.  
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24 The study included a total of 5821 patients, of which 3766 patients completed a 3-day  
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26 micturition diary both pre-treatment and at least once after initiation of treatment, apparently  
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28 reflecting clinical practice in Germany. Our analysis is based upon the latter group only to  
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30 ascertain validity of the reported voiding data, but the demographic characteristics including  
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32 the presence of potential risk factors were very similar in the total population and those with  
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34 documented micturition diaries (data not shown). Our analysis is based upon the office visit  
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36 prior to and at the end of the observational period; in cases of premature study discontinuation,  
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38 the data from the last available visit were used in a last-observation-carried-forward manner.  
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45 At the initial visit, a medical history including questions about the possible risk factors of  
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47 smoking, alcohol and caffeine use was recorded in a standardized manner. BMI was  
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49 calculated from the height and weight of the patient. The physician applied qualitative scoring  
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51 to record smoking status (never smoked, past smoker and present smoker), alcohol  
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53 consumption (abstinent, light, moderate, strong) and caffeine intake (none, moderate, strong)  
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55 based upon information provided by the patient. This information was used to stratify the  
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57 population for all further analyses, but no instructions were given on how to rate these factors  
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3 in order not to minimize interference with the observational character of the study. Moreover,  
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5 at each visit the intensity of OAB symptoms (based upon diaries), a problem assessment  
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7 (“The overactive bladder presently causes no/mild/moderate/severe problems”), possible  
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9 adverse events and prescribed darifenacin dose were recorded. At the final visit, global  
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11 physician assessments of efficacy and tolerability and patient-reported satisfaction with  
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13 treatment and alteration in the ability to hold urine were also documented.  
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20 Data handling was performed by a contract research organization (Dr. Schauerte,  
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22 Oberhaching, Germany). Baseline data are presented as means  $\pm$  SD of absolute values of n  
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24 patients. In line with previous similar analyses (28), treatment data are presented as %  
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26 changes for OAB symptoms. Adverse events were coded according to MedDRA Version 8.1.  
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28 Descriptive statistical analysis was performed with the SAS for Windows program package  
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30 (version 9.1). For interval-scaled variables, multiple ordinary least squares regression was  
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32 applied, and logistic regression models for dichotomous dependent variables. As independent  
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34 variables, BMI ( $\text{kg}/\text{m}^2$ ), age (years), and factors of gender, alcohol consumption, smoking and  
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36 caffeine intake were entered into the models to explore the statistical contribution of these  
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38 factors to treatment responses. A  $p < 0.05$  was considered significant.  
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## 45 RESULTS

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50 The study population had an average age of  $62.6 \pm 12.8$  years, body weight of  $75.8 \pm 12.0$  kg,  
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52 height of  $168.5 \pm 7.2$  cm and BMI of  $26.7 \pm 4.0$   $\text{kg}/\text{m}^2$ . Among them 77.1% were female,  
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54 75.3% non-smokers, 16.8% present smokers and 7.9% past smokers. Abstinence, light,  
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56 moderate and strong alcohol consumption was reported by 28.7%, 58.3%, 12.6% and 0.5% of  
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58 participants, respectively (the latter two being pooled for all further analysis). No, moderate or  
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3 strong caffeine consumption was reported by 11.8%, 80.6% and 7.6%, respectively. The  
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5 patients reported OAB symptoms for <1, 1-5, 6-10 and > 10 years in 26.0%, 54.7%, 14.2%  
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7 and 5.2%, respectively. 56.4% of patients had received some type of OAB treatment in the  
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9 past. At enrolment 31.7% used pads, 27.9% toilet training, 34.4% pelvic floor exercises and  
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11 4.2% electrostimulation (multiple nominations possible), whereas no adjunct treatments for  
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13 voiding dysfunction were reported by 32.3%. The prevalence of concomitant urological  
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15 medication (WHO Drug Directory class G04) was <5%. A darifenacin starting dose of 7.5  
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17 and 15 mg q.d. was used in 97.2% and 2.8%, respectively. The episode frequency of urgency,  
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19 incontinence, micturitions and nocturia as well as problem assessment before and after  
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21 treatment are shown in figure 1. Ability to hold urine after treatment as compared to the start  
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23 of treatment was rated as significantly longer, longer, same or shorter by 46.9%, 40.2%,  
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25 12.2% and 0.6% of patients, respectively. The global efficacy of treatment was rated as very  
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27 good, good, moderate or insufficient by 42.7%, 36.1%, 10.3% and 10.9%, respectively. **At the**  
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29 **end of the observation period 84.7% and 15.3% of patients received the 7.5 and 15 mg dose of**  
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31 **darifenacin, respectively. Gender and smoking status had little association with dose selection,**  
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33 **whereas greater age (15 mg used by 14.4% aged <50 years vs. 17.1% >75 years), BMI**  
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35 **(13.9% for <25 kg/m<sup>2</sup> vs. 21.7% for >30 kg/m<sup>2</sup>) or alcohol consumption (15.7% for abstinent**  
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37 **patients vs. 18.3% for those reporting moderate-strong consumption) were associated with a**  
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39 **higher probability of receiving the 15 mg dose; in contrast, coffee consumption of any degree**  
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41 **was associated with a smaller probability for receiving the higher dose (14.6% vs. 20.5%).**  
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53 Based upon the data from the overall population, multiple regression models were applied to  
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55 explore the roles of various factors in treatment-associated improvements of urgency,  
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57 incontinence, micturition and nocturia episodes (Table 1). The baseline episode frequency of  
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59 a symptom was the strongest predictor of its treatment-associated improvement (Table 1).  
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3 Increasing age was significantly correlated to decreased improvements in urgency,  
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5 incontinence, daytime micturition and nocturia episodes, but the magnitude of the age effect  
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7 was very small relative to the overall treatment effect. For example, darifenacin treatment was  
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9 associated with a reduction in the number of urgency episodes/24 h from  $9.1 \pm 5.8$  to  $5.0 \pm 4.1$ ,  
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11 whereas each additional year of age was statistically associated with a decreased improvement  
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13 of 0.01 episodes. Female gender did not significantly affect treatment-associated  
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15 improvements of incontinence episodes but was associated with a statistically greater  
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17 improvement of urgency, micturition and nocturia episodes (Table 1). However, the  
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19 correlation of gender with the overall improvement was relatively weak. Except for a small  
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21 but significant effect of increasing BMI on the improvement of urgency episodes, none of the  
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23 life style factors significantly affected improvements of any of the four OAB symptoms  
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(Table 1).

In line with the results from the above linear models regarding OAB symptoms, increasing age was also associated with a significantly smaller likelihood for a positive problem assessment and global efficacy or tolerability rating, whereas female gender was associated with a significantly greater likelihood for a positive problem assessment or global efficacy rating, but here as well effect sizes were small (Table 2). None of the life style factors significantly affected problem assessment or global efficacy (Table 2).

In line with post-marketing studies on other muscarinic receptor antagonists (7, 8, 29), adverse events were noted in only 2.7% of patients and consisted largely of dry mouth and constipation. Accordingly, the global tolerability was rated as very good, good, moderate and poor by 50.1%, 43.6%, 4.6% and 1.8% of patients, respectively, and the overall patient satisfaction was reported as very satisfied, satisfied or not satisfied by 42.4%, 44.9% and

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3 12.7%, respectively. In multiple linear models none of the life style factors was associated  
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6 with an altered global tolerability rating (Table 2).  
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## 10 DISCUSSION 11

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15 Age as well as several life style factors have been reported to be potential risk factors for  
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17 OAB (see introduction). While female gender has not been established as a risk factor for  
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19 OAB, the majority of patients receiving OAB treatment are female (7, 8). Limited clinical  
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21 data have explored the effects of age and gender on treatment responses in OAB patients (7,  
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23 24), but the potential effects of life-style factors have not been reported to our knowledge.  
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### 29 Critique of methods 30

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34 Our analysis is based upon an observational, large-scale, open-label study on the efficacy and  
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36 tolerability of darifenacin in routine clinical use. In the absence of a placebo group,  
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38 observational data do not allow for absolute conclusions about the safety and efficacy of  
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40 darifenacin. However, multiple placebo-controlled studies have already demonstrated the  
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42 absolute efficacy and tolerability of darifenacin (25-27). On the other hand, observational  
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44 studies have proven useful for comparisons of relative efficacy and tolerability between  
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46 patient groups of OAB patients (7, 8, 24). An observational study from routine clinical use  
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48 may be particularly advantageous to explore the roles of potential OAB risk factors in  
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50 treatment responses, because the strict inclusion and exclusion criteria of randomized  
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52 controlled studies may limit variability of these factors in the study population, particularly  
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54 for life style factors. Moreover, the expected inter-relatedness of several risk factors, e.g. of  
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56 smoking and alcohol use, requires large patient numbers to yield the necessary statistical  
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3 power for detection of minor effects. Such large patient numbers are easier to collect from  
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5 observational studies.  
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10 On the other hand, for reason of practicality, assessments in post-marketing surveillance  
11 studies are somewhat cruder than in controlled clinical or dedicated epidemiological studies.  
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13 For example, the quantitative assessment of life style factors is everything but straightforward,  
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15 particularly when it comes to factors such as alcohol consumption where many patients may  
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17 provide somewhat “beautified” responses. Given the practical limitations of a large and non-  
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19 interventional study we had chosen for an assessment graded by the physician into 3-4  
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21 categories. While this may be suboptimal for a dedicated study into e.g. alcohol consumption,  
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23 it reflects a necessary compromise between the scientifically desirable and the practically  
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25 feasible. Finally, we have also used physician ratings of global efficacy and tolerability, as  
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27 particularly the latter has proven to yield a statistically sensitive means to pick up differences  
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29 in tolerability despite a typically reported incidence of adverse events in observational studies  
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31 in OAB (7, 8). These specific advantages and limitations should be kept in mind in the  
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33 interpretation of our data.  
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#### 43 Treatment results

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48 Age not only is a well-established risk factor for OAB (2-4) but is also known to affect the  
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50 expression of muscarinic receptors in the bladder and other tissues including salivary glands  
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52 and heart (23, 30). Until now only limited data on the effects of age on treatment results in  
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54 OAB patients had been reported: One large observational study with tolterodine demonstrated  
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56 a statistically significant but probably clinically irrelevant adverse effect of age on treatment-  
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58 associated symptom improvement and global efficacy (7). On the other hand, this small  
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3 negative effect was compensated by increasing severity of baseline symptoms with age and  
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5 the strong statistical effect of baseline symptoms on the overall improvement. The present  
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7 data for darifenacin also report a statistically significant but very small negative effect of age  
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9 on treatment-associated improvements of OAB symptoms and global efficacy. This may even  
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11 be somewhat under-estimated due to a trend for a higher dose with increasing age. While age  
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13 did not significantly affect the global tolerability of tolterodine (7), it was shown to have a  
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15 statistically significant but very small adverse effect on the tolerability of solifenacin (8).  
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17 Very similar findings were obtained in the present study with darifenacin. Therefore, the  
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19 overall data show that muscarinic receptor antagonists have similar efficacy across all age  
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21 groups. The overall tolerability may decline with increasing age, but this may reflect the  
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23 overall health status of the elderly rather than specific treatment-related adverse effects.  
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32 Although women receive muscarinic antagonist treatment of OAB symptoms more frequently  
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34 than men, the prevalence of OAB does not exhibit major gender differences (2-4) and  
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36 muscarinic receptor expression in the bladder is similar in both genders across multiple  
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38 species (23). An observational study with tolterodine has reported that gender may have  
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40 statistically significant effects on therapeutic efficacy, which are very small and not seen for  
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42 all OAB symptoms; moreover, gender did not significantly affect the tolerability of  
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44 tolterodine (7). Gender did not affect the efficacy or tolerability of solifenacin in a similar  
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46 study (24). In line with these observations, the present study found very similar effects in both  
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48 genders upon treatment with darifenacin. Therefore, it appears that muscarinic antagonists as  
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50 a class are similarly effective and tolerated in male and female OAB patients.  
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58 The major novel aspect of the present analysis was the exploration of potential effects of life  
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60 style factors on the efficacy and tolerability of a muscarinic antagonist in the treatment of

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3 OAB. While a high BMI has been demonstrated as a risk factor for OAB (see introduction),  
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5 our data demonstrate that it does not affect the efficacy or tolerability of darifenacin in a  
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7 clinically relevant manner. This is interesting as obesity and treatment response could not  
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9 only interfere pathophysiologically but also a greater body weight would be associated with a  
10  
11 smaller drug exposure per kg body weight. Accordingly, a greater BMI was associated with a  
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13 greater likelihood for a higher darifenacin dose in the present study. While the role of alcohol,  
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15 smoking and caffeine intake as risk factors for OAB remains under debate (see introduction),  
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17 neither affected the efficacy or tolerability of darifenacin in the present study, although a trend  
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19 for a higher darifenacin dose with greater alcohol (but not smoking or coffee) consumption  
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21 may have masked an effect of alcohol on treatment.  
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## 29 CONCLUSION

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34 In conclusion, the available data show that age, gender and several life style factors have no  
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36 clinically relevant impact on the efficacy or tolerability of the muscarinic receptor antagonist  
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38 darifenacin. Thus, muscarinic receptor antagonists can be expected to be similarly effective  
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40 and tolerated regardless of the presence of such factors. While only limited data are available  
41  
42 with regard to the modification of life style factors to improve OAB symptoms (19, 20), we  
43  
44 propose that an optimal therapeutic approach to OAB will involve both medical treatment and  
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46 life style advice.  
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53 Acknowledgements: Bayer Vital had funded the underlying study as well as the present  
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55 analyses.  
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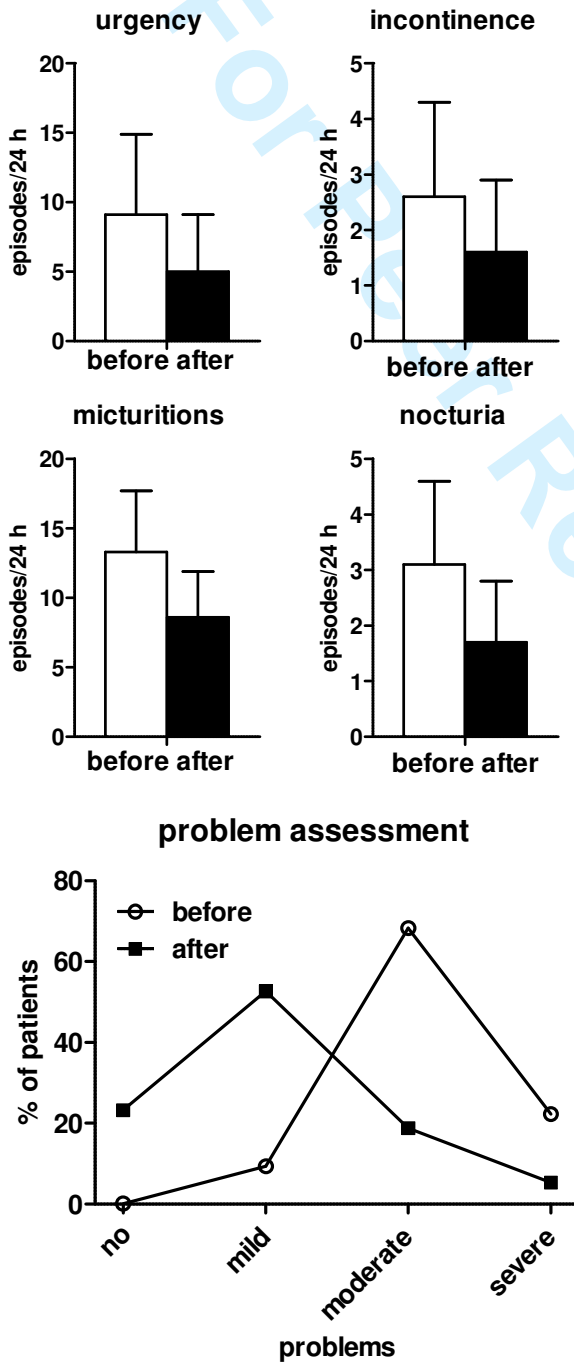
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## LEGENDS TO THE FIGURES

Figure 1: OAB symptoms and problem assessment at baseline and after treatment with darifenacin. Data are means  $\pm$  SD except for problem assessment.



## TABLES

**Table 1:** Multiple regression models exploring the effects of potential risk factors for darifenacin treatment-associated improvement of OAB symptoms. A positive number for the parameter indicates a numerically worse result, and a negative number a numerically better result. Data are means  $\pm$  SD. P-values are based on a Wald Chi-square test.

	Parameter estimate	p-value
Urgency episode improvement		
<b>Age, per year</b>	<b>0.0127 <math>\pm</math> 0.0045</b>	<b>0.0049</b>
<b>Gender, relative to male</b>	<b>-0.4416 <math>\pm</math> 0.1379</b>	<b>0.0014</b>
<b>BMI, per kg/m<sup>2</sup></b>	<b>0.0298 <math>\pm</math> 0.0146</b>	<b>0.0421</b>
Previous smoking, relative to none	-0.0128 $\pm$ 0.2124	0.9521
Current smoking, relative to none	0.2335 $\pm$ 0.1575	0.1382
Mild alcohol, relative to none	-0.1812 $\pm$ 0.1325	0.1715
Moderate to severe alcohol, relative to none	-0.1920 $\pm$ 0.2008	0.3391
Moderate caffeine, relative to none	-0.1372 $\pm$ 0.1747	0.4325
Severe caffeine, relative to none	0.4276 $\pm$ 0.2647	0.1063
Baseline urgency, per episode	0.5047 $\pm$ 0.0097	<0.0001
Incontinence episode improvement		
<b>Age, per year</b>	<b>0.0047 <math>\pm</math> 0.0020</b>	<b>0.0210</b>
Gender, relative to male	-0.0011 $\pm$ 0.0659	0.9863
BMI, per kg/m <sup>2</sup>	0.0116 $\pm$ 0.0065	0.0727
Previous smoking, relative to none	-0.1764 $\pm$ 0.1016	0.0827
Current smoking, relative to none	0.0994 $\pm$ 0.0708	0.1607

Mild alcohol, relative to none	$0.0261 \pm 0.0586$	0.6562
Moderate to severe alcohol, relative to none	$0.0803 \pm 0.0903$	0.3739
Moderate caffeine, relative to none	$-0.1041 \pm 0.0773$	0.1779
Severe caffeine, relative to none	$0.1131 \pm 0.1203$	0.3470
Baseline incontinence, per episode	$0.3948 \pm 0.0133$	<0.0001
Micturition episode improvement		
<b>Age, per year</b>	<b><math>0.0190 \pm 0.0042</math></b>	<b>&lt;0.0001</b>
<b>Gender, relative to male</b>	<b><math>-0.3316 \pm 0.1247</math></b>	<b>0.0079</b>
BMI, per kg/m <sup>2</sup>	$0.0219 \pm 0.0134$	0.1012
Previous smoking, relative to none	$0.0224 \pm 0.1897$	0.9060
Current smoking, relative to none	$0.1535 \pm 0.1445$	0.2880
Mild alcohol, relative to none	$-0.1047 \pm 0.1215$	0.3889
Moderate to severe alcohol, relative to none	$0.0744 \pm 0.1842$	0.6861
Moderate caffeine, relative to none	$-0.2001 \pm 0.1597$	0.2104
Severe caffeine, relative to none	$0.2477 \pm 0.2430$	0.3081
Baseline micturitions, per episode	$0.4623 \pm 0.0115$	<0.0001
Nocturia episode improvement		
<b>Age, per year</b>	<b><math>0.0097 \pm 0.0014</math></b>	<b>&lt;0.0001</b>
<b>Gender, relative to male</b>	<b><math>-0.1638 \pm 0.0423</math></b>	<b>0.0001</b>
BMI, per kg/m <sup>2</sup>	$0.0085 \pm 0.0045$	0.0608
Previous smoking, relative to none	$-0.0317 \pm 0.0645$	0.6231
Current smoking, relative to none	$0.0897 \pm 0.0491$	0.0677
Mild alcohol, relative to none	$-0.0693 \pm 0.04121$	0.0927
Moderate to severe alcohol, relative to none	$-0.0659 \pm 0.0626$	0.2925

Moderate caffeine, relative to none	$-0.0910 \pm 0.0544$	0.0946
Severe caffeine, relative to none	$0.0454 \pm 0.0826$	0.5828
Baseline nocturia, per episode	$0.3880 \pm 0.0120$	<0.0001

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**Table 2:** Logistic regression models exploring the effects of potential risk factors for darifenacin treatment-associated improvement of problem assessment and the global efficacy and tolerability of darifenacin. Data are shown as odds ratios for a beneficial effect (greater improvement of problem assessment, very good or good global efficacy and tolerability) with 95% confidence intervals in parentheses (intervals excluding unity indicate statistical significance). In this regard an odds ratio > 1 indicates a numerically better result, and an odds ratio < 1 a numerically worse result.

	Problem assessment (improvement vs. no improvement)	Efficacy (very good/good vs. moderate/poor)	Tolerability (very good/good vs. moderate/poor)
Age, per year	<b>0.981 (0.975; 0.988)</b>	<b>0.978 (0.970; 0.985)</b>	<b>0.982 (0.971; 0.993)</b>
Gender, relative to male	<b>1.313 (1.087; 1.587)</b>	<b>1.396 (1.135; 1.716)</b>	1.047 (0.746; 1.471)
BMI, per kg/m <sup>2</sup>	1.010 (0.990; 1.032)	0.979 (0.957; 1.001)	0.998 (0.963; 1.034)
Previous smoking, relative to none	1.114 (0.823; 1.508)	0.950 (0.690; 1.309)	1.074 (0.615; 1.877)
Current smoking, relative to none	0.870 (0.695; 1.089)	0.923 (0.719; 1.186)	0.739 (0.501; 1.090)
Mild alcohol, relative to none	1.037 (0.858; 1.253)	1.036 (0.840; 1.277)	1.371 (0.998; 1.883)
Moderate to severe alcohol, relative to none	0.951 (0.717; 1.263)	0.952 (0.698; 1.298)	1.429 (0.863; 2.364)

Moderate caffeine, relative to none	1.261 (0.989; 1.608)	1.125 (0.858; 1.474)	1.224 (0.818; 1.830)
Severe caffeine, relative to none	1.073 (0.738; 1.561)	0.840 (0.559; 1.262)	1.052 (0.556; 1.992)

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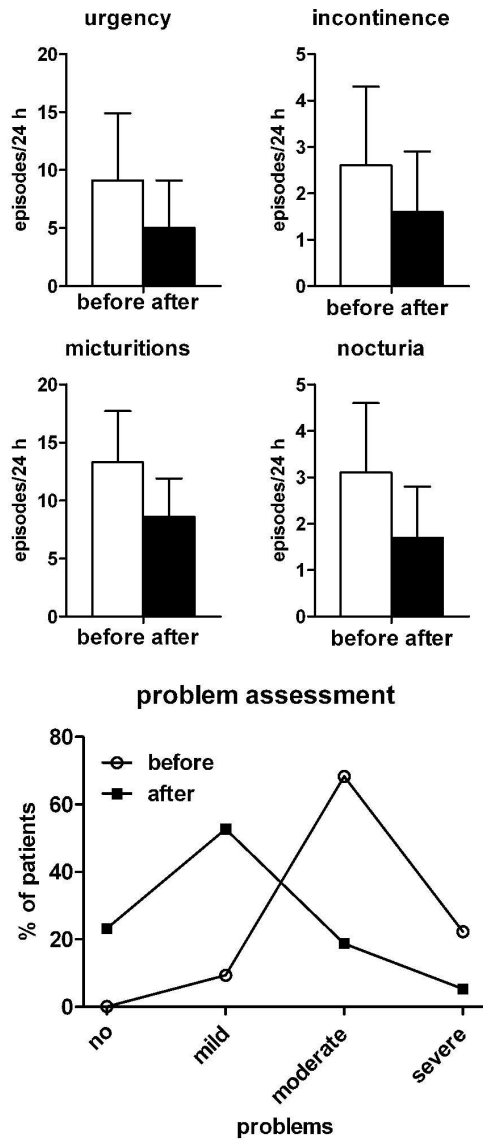


Figure 1  
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