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EFFECTS OF CONCOMITANT DIABETES ON TREATMENT RESPONSES TO A MUSCARINIC ANTAGONIST IN OVERACTIVE BLADDER PATIENTS

Hypothesis / aims of study

The overactive bladder syndrome (OAB) and diabetes are common in the general population and the prevalence of both increases with age. Hence, a considerable fraction of OAB patients suffer from concomitant diabetes. This comorbidity may exist even more often than to be expected based on chance alone as diabetes itself can impair bladder function. Based on such diabetes-induced impairments, OAB may be more difficult to treat in diabetic patients but surprisingly this has not been investigated to our knowledge. Therefore, we have explored this question using the muscarinic antagonist darifenacin as an example.

Study design, materials and methods

This is a post-hoc analysis of a large observational study into the safety and efficacy of darifenacin. Thus, no specific inclusion and exclusion criteria were applied other than a minimum age of 18 years and the recommendations from the Summary of Product Characteristics for darifenacin. The participating 1155 physicians (largely board-certified, office-based urologists) were asked to systematically record their observation of patients receiving darifenacin (7.5 or 15 mg/d) based upon their medical judgment. The planned observation time was 12 weeks. For the purpose of the current analysis, two groups of patients from this study were considered, those without documented comorbidities (n = 1291, “control”) and those with concomitant diabetes (n = 524). Our analysis is based upon the office visit prior to and at the end of the observational period; in cases of premature study discontinuation, the data from the last available visit were used in a last-observation-carried-forward manner. Data are presented as means ± SD, except for categorical variables, of n patients. Descriptive statistical analysis was performed with the SAS for Windows programme package (version 9.1). For interval-scaled variables, multiple ordinary least squares regression was applied, and logistic regression models for dichotomous dependent variables. As independent variable, the presence of diabetes and, where applicable, the pre-treatment value of a given parameter was entered into the models to explore their statistical contribution to treatment responses. As a previous analysis of the same database had explored possible contributions of gender, age, body mass index, smoking status and alcohol and caffeine consumption to treatment responses, these factors were also entered into the models as additional independent variables. A $p < 0.05$ was considered significant. Post-hoc power calculations for the least affected symptom indicate an 80% power to detect a group difference of 0.24 episodes.

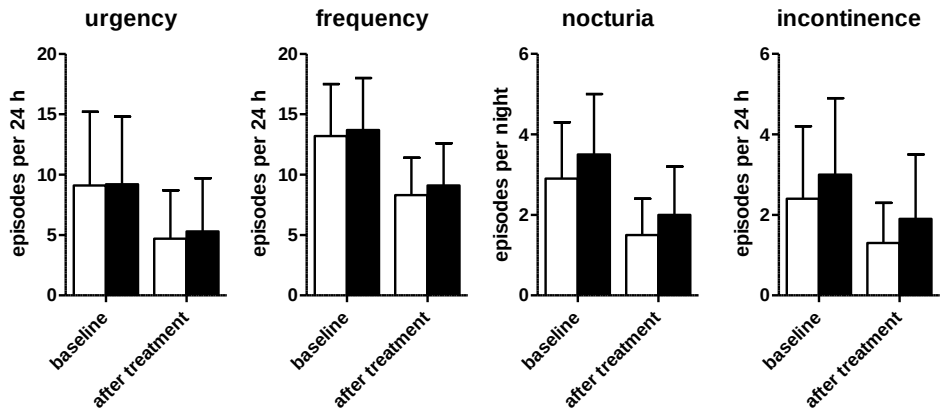
Results

Patients with concomitant diabetes differed considerably in their demographic characteristics from those without documented comorbidities (Table 1) but baseline episode frequency of OAB symptoms was rather similar (Figure 1). While the starting dose of darifenacin was similar in both groups (>95% at 7.5 mg/d), diabetic patients were more likely to receive dose-escalation during treatment (19.1% vs. 11.1% at 15 mg/d at last follow-up). Symptom episode frequency after treatment was similar in both groups (Figure 1). In the multiple regression models, baseline values expectedly had the largest impact on post-treatment data. Thus, each episode more at baseline was associated with 0.47, 0.42, 0.38 and 0.34 episodes, respectively, more remaining after treatment. In contrast, the additional effect of diabetes was associated with only a small unfavourable effect on symptom episode frequency after treatment (0.55, 0.61, 0.25 and 0.36 more episodes of urgency, frequency, nocturia and incontinence, respectively, remaining after treatment; $p < 0.05$ in all cases). Accordingly, ratings on the problem improvement scale did not differ significantly between groups in logistic regression models. The reported adverse event frequency was 2.1% in both groups. Global tolerability estimates did not differ significantly between groups in logistic regression models.

Table 1: Baseline characteristics of control and diabetic OAB patients

	Control	Diabetes
Gender, % female	83.0	76.3
Age, years	57.3 ± 12.8	67.2 ± 10.8
Body weight, kg	73.4 ± 11.5	79.4 ± 12.1
Body mass index, kg/m^2	25.7 ± 3.7	28.1 ± 4.2
Smoking, % never/present/past	74.8/18.0/7.2	72.7/17.8/9.5
Alcohol consumption, % abstinent/little/moderate-severe	27.9/62.0/10.2	28.8/57.5/13.4
Caffeine consumption, % none/moderate/severe	12.7/79.6/7.8	10.5/80.7/8.8
OAB history, % <1/1-5/>5 years	34.4/52.3/13.3	18.7/55.3/26.1
Concomitant medications, % yes	5.5	82.3

Figure 1: OAB symptom episode frequency in control (open bars) and diabetic patients (filled bars) at baseline and last follow-up



Interpretation of results

This observational study should not be misinterpreted as a measure of efficacy or safety of darifenacin in absolute terms. However, against the background of many placebo-controlled studies with this drug, it can be used to compare treatment outcomes in two groups of patients. Of note, we are not aware of any previous study exploring treatment efficacy of a muscarinic antagonist in diabetic as compared to non-diabetic patients, and our approach may be the only feasible one to address this question.
As the two groups differed in several baseline parameters including age and gender, multiple regression models have been applied to provide adjusted effect size estimates for the concomitant presence of diabetes on treatment results. While these models indicated statistically significant post treatment differences between diabetic and control OAB patients, the magnitude of the effect sizes was small relative to the overall treatment effects. Accordingly, patient-reported outcomes such as global efficacy and problem rating were not significantly affected by the presence of diabetes.

Concluding message

We conclude that the efficacy and safety of a muscarinic antagonist such as darifenacin does not differ in a clinically relevant manner between diabetic and control OAB patients. We propose that muscarinic antagonists are similarly suitable for OAB patients with and without diabetes.

Specify source of funding or grant	**Bayer Vital has funded the underlying study as well as the present analyses.**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**No**
Is this a Randomised Controlled Trial (RCT)?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**No**
This study did not require ethics committee approval because	**At the time the study was performed, ethical committee approval, registration in clinical trials databases or written patient consent were neither required nor recommended for purely observational studies, such as this one, in Germany.**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**No**