



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

Journal:	<i>International Journal of Clinical Practice</i>
Manuscript ID:	IJCP-02-10-0091.FT10.R1
Manuscript Type:	Original Paper
Date Submitted by the Author:	15-Mar-2010
Complete List of Authors:	Schneider, Tim; Praxisklinik Urologie Rhein-Ruhr Marschall-Kehrel, Daniela; Urological Practice Hanisch, Jens Ulrich; Bayer Vital, Dept. Non-Interventional Studies Michel, Martin; AMC, University of Amsterdam, Dept. Pharmacology & Pharmacotherapy
Specialty area:	



1
2
3 Do gender, age or life style factors affect responses to anti-muscarinic treatment in overactive
4
5 bladder patients?
6
7
8
9

10
11
12 Tim Schneider^a, Daniela Marschall-Kehrel^b, Jens U. Hanisch^c, Martin C. Michel^d
13
14

15
16
17 ^aPraxisklinik Urologie Rhein-Ruhr, Mülheim, Germany
18

19 ^bUrological Practice, Frankfurt, Germany
20

21 ^cDept. Non-Interventional Studies, Bayer Vital GmbH, Wuppertal, Germany
22

23 ^dDept. Pharmacology & Pharmacotherapy, Academic Medical Center, Amsterdam,
24
25 Netherlands
26
27

28
29
30
31 Address for correspondence:
32

33
34 Prof. Martin C. Michel
35

36 Dept. Pharmacology & Pharmacotherapy
37

38 Academic Medical Center
39

40 Meibergdreef 15
41

42 1105 AZ Amsterdam, Netherlands
43

44
45 phone: +31-20-566-6762
46

47
48 fax: +31-20-696-5976
49

50
51 mail: m.c.michel@amc.nl
52
53

54
55 Author contributions
56

57 All authors jointly developed the idea for the analyses underlying the present manuscript. The
58
59 data had been collected by 1155 German physicians and were analyzed by a contract research
60

1
2
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
7 scientific content by **Daniela Marschall-Kehrel** and **Jens U. Hanisch**. Bayer Vital had funded
8
9 the underlying study as well as the present analyses. Authors had access to the study data that
10
11 support the publication.
12
13
14

15
16
17 Disclosures: Bayer Vital had funded the underlying study as well as the present analyses. **Tim**
18
19 **Schneider** has received consultancy and/or speaker honoraria from Astellas, Bayer and Pfizer,
20
21 **Daniela Marschall-Kehrel** has received consultancy honoraria from Allergan, Apogepha,
22
23 Astellas, Bayer, Ferring, Lilly, and Pfizer. **Jens U. Hanisch** is an employee and stock owner of
24
25 Bayer. **Martin C. Michel** has received research funds, speaker and/or consultancy honoraria
26
27 from Allergan, Astellas, Bayer, Lilly and Pfizer.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 ABSTRACT
4
5
6
7

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.
13
14
15
16
17
18
19
20
21

22 Methods: Data were analyzed from 3766 OAB patients (77.1% female, age 62.6 ± 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.
28
29
30
31
32
33
34
35
36
37
38

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.
45
46
47
48
49
50
51
52
53
54

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.
58
59
60

1
2
3
4
5
6 Key words: overactive bladder, urinary incontinence, gender, age, obesity, smoking, alcohol,
7
8 caffeine, darifenacin
9

10
11
12 What is already known about this topic?
13

14
15 Gender, age, obesity, smoking, and alcohol or caffeine intake have been shown or proposed to
16
17 be risk factors for the prevalence and/or severity of the overactive bladder symptom complex
18
19 (OAB) or related parameters but their possible effect on treatment outcomes is unknown.
20
21

22
23
24 What does this article add?
25

26
27 Gender, age, obesity, smoking, and alcohol or caffeine intake apparently have little effect on
28
29 the results of OAB treatment with a muscarinic antagonist.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 the possibility to improve the condition (18). For example, a recent randomized trial has
4
5 demonstrated that alterations of fluid intake can affect symptoms in OAB patients (19)
6
7
8 whereas weight loss may improve incontinence in obese patients (20).
9

10
11
12 Muscarinic receptor antagonists are the main treatment option for OAB patients (21, 22).

13
14
15 While they have consistently been shown to be superior to placebo, it remains unclear how
16
17 potential risk factors for OAB may affect the treatment response to these drugs. For example,
18
19 age may alter the expression of muscarinic receptors in the bladder and its responsiveness to
20
21 muscarinic receptor ligands (23), but some clinical data indicate that age may have limited
22
23 effect on treatment responses (7, 24). Whether modifiable factors such as obesity, smoking or
24
25 alcohol and caffeine ingestion may affect the therapeutic response to muscarinic antagonists
26
27 has not been investigated to our knowledge.
28
29
30
31
32
33

34 Darifenacin is a muscarinic receptor antagonist with efficacy in the treatment of OAB
35
36 symptoms in several randomized, double-blind, placebo-controlled studies (25-27). Against
37
38 the above background, we have used the database from a recent large observational study of
39
40 the safety and efficacy of darifenacin to explore possible roles of gender, age and life-style
41
42 factors in the clinical response to a muscarinic receptor antagonist.
43
44
45
46
47

48 MATERIAL AND METHODS

49
50
51
52

53 This manuscript describes a post-hoc analysis of a large, open-label, observational study into
54
55 the safety and efficacy of darifenacin which had been performed as part of its post-marketing
56
57 surveillance in Germany. Thus, no specific inclusion and exclusion criteria were applied other
58
59 than a minimum age of 18 years and the recommendations from the Summary of Product
60

1
2
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
5
6 systematically record their observation of patients receiving darifenacin based upon their
7
8 medical judgment. Based upon the package insert, recommended darifenacin doses were 7.5
9
10 and 15 mg q.d. The planned observation time was 12 weeks. At the time the study was
11
12 performed, ethical committee approval, registration in clinical trials databases or written
13
14 patient consent were neither required nor recommended for purely observational studies, such
15
16 as this one, in Germany.
17
18
19
20
21
22
23

24 The study included a total of 5821 patients, of which 3766 patients completed a 3-day
25
26 micturition diary both pre-treatment and at least once after initiation of treatment, apparently
27
28 reflecting clinical practice in Germany. Our analysis is based upon the latter group only to
29
30 ascertain validity of the reported voiding data, but the demographic characteristics including
31
32 the presence of potential risk factors were very similar in the total population and those with
33
34 documented micturition diaries (data not shown). Our analysis is based upon the office visit
35
36 prior to and at the end of the observational period; in cases of premature study discontinuation,
37
38 the data from the last available visit were used in a last-observation-carried-forward manner.
39
40
41
42
43
44

45 At the initial visit, a medical history including questions about the possible risk factors of
46
47 smoking, alcohol and caffeine use was recorded in a standardized manner. BMI was
48
49 calculated from the height and weight of the patient. The physician applied qualitative scoring
50
51 to record smoking status (never smoked, past smoker and present smoker), alcohol
52
53 consumption (abstinent, light, moderate, strong) and caffeine intake (none, moderate, strong)
54
55 based upon information provided by the patient. This information was used to stratify the
56
57 population for all further analyses, but no instructions were given on how to rate these factors
58
59
60

1
2
3 in order not to minimize interference with the observational character of the study. Moreover,
4
5 at each visit the intensity of OAB symptoms (based upon diaries), a problem assessment
6
7 (“The overactive bladder presently causes no/mild/moderate/severe problems”), possible
8
9 adverse events and prescribed darifenacin dose were recorded. At the final visit, global
10
11 physician assessments of efficacy and tolerability and patient-reported satisfaction with
12
13 treatment and alteration in the ability to hold urine were also documented.
14
15
16
17
18
19

20 Data handling was performed by a contract research organization (Dr. Schauerte,
21
22 Oberhaching, Germany). Baseline data are presented as means \pm SD of absolute values of n
23
24 patients. In line with previous similar analyses (28), treatment data are presented as %
25
26 changes for OAB symptoms. Adverse events were coded according to MedDRA Version 8.1.
27
28 Descriptive statistical analysis was performed with the SAS for Windows program package
29
30 (version 9.1). For interval-scaled variables, multiple ordinary least squares regression was
31
32 applied, and logistic regression models for dichotomous dependent variables. As independent
33
34 variables, BMI (kg/m^2), age (years), and factors of gender, alcohol consumption, smoking and
35
36 caffeine intake were entered into the models to explore the statistical contribution of these
37
38 factors to treatment responses. A $p < 0.05$ was considered significant.
39
40
41
42
43
44

45 RESULTS

46
47
48
49

50 The study population had an average age of 62.6 ± 12.8 years, body weight of 75.8 ± 12.0 kg,
51
52 height of 168.5 ± 7.2 cm and BMI of 26.7 ± 4.0 kg/m^2 . Among them 77.1% were female,
53
54 75.3% non-smokers, 16.8% present smokers and 7.9% past smokers. Abstinence, light,
55
56 moderate and strong alcohol consumption was reported by 28.7%, 58.3%, 12.6% and 0.5% of
57
58 participants, respectively (the latter two being pooled for all further analysis). No, moderate or
59
60

1
2
3 strong caffeine consumption was reported by 11.8%, 80.6% and 7.6%, respectively. The
4
5 patients reported OAB symptoms for <1, 1-5, 6-10 and > 10 years in 26.0%, 54.7%, 14.2%
6
7 and 5.2%, respectively. 56.4% of patients had received some type of OAB treatment in the
8
9 past. At enrolment 31.7% used pads, 27.9% toilet training, 34.4% pelvic floor exercises and
10
11 4.2% electrostimulation (multiple nominations possible), whereas no adjunct treatments for
12
13 voiding dysfunction were reported by 32.3%. The prevalence of concomitant urological
14
15 medication (WHO Drug Directory class G04) was <5%. A darifenacin starting dose of 7.5
16
17 and 15 mg q.d. was used in 97.2% and 2.8%, respectively. The episode frequency of urgency,
18
19 incontinence, micturitions and nocturia as well as problem assessment before and after
20
21 treatment are shown in figure 1. Ability to hold urine after treatment as compared to the start
22
23 of treatment was rated as significantly longer, longer, same or shorter by 46.9%, 40.2%,
24
25 12.2% and 0.6% of patients, respectively. The global efficacy of treatment was rated as very
26
27 good, good, moderate or insufficient by 42.7%, 36.1%, 10.3% and 10.9%, respectively. **At the**
28
29 **end of the observation period 84.7% and 15.3% of patients received the 7.5 and 15 mg dose of**
30
31 **darifenacin, respectively. Gender and smoking status had little association with dose selection,**
32
33 **whereas greater age (15 mg used by 14.4% aged <50 years vs. 17.1% >75 years), BMI**
34
35 **(13.9% for <25 kg/m² vs. 21.7% for >30 kg/m²) or alcohol consumption (15.7% for abstinent**
36
37 **patients vs. 18.3% for those reporting moderate-strong consumption) were associated with a**
38
39 **higher probability of receiving the 15 mg dose; in contrast, coffee consumption of any degree**
40
41 **was associated with a smaller probability for receiving the higher dose (14.6% vs. 20.5%).**
42
43
44
45
46
47
48
49
50
51
52

53 Based upon the data from the overall population, multiple regression models were applied to
54
55 explore the roles of various factors in treatment-associated improvements of urgency,
56
57 incontinence, micturition and nocturia episodes (Table 1). The baseline episode frequency of
58
59 a symptom was the strongest predictor of its treatment-associated improvement (Table 1).
60

1
2
3 Increasing age was significantly correlated to decreased improvements in urgency,
4
5 incontinence, daytime micturition and nocturia episodes, but the magnitude of the age effect
6
7 was very small relative to the overall treatment effect. For example, darifenacin treatment was
8
9 associated with a reduction in the number of urgency episodes/24 h from 9.1 ± 5.8 to 5.0 ± 4.1 ,
10
11 whereas each additional year of age was statistically associated with a decreased improvement
12
13 of 0.01 episodes. Female gender did not significantly affect treatment-associated
14
15 improvements of incontinence episodes but was associated with a statistically greater
16
17 improvement of urgency, micturition and nocturia episodes (Table 1). However, the
18
19 correlation of gender with the overall improvement was relatively weak. Except for a small
20
21 but significant effect of increasing BMI on the improvement of urgency episodes, none of the
22
23 life style factors significantly affected improvements of any of the four OAB symptoms
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
(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

1
2
3 12.7%, respectively. In multiple linear models none of the life style factors was associated
4
5
6 with an altered global tolerability rating (Table 2).
7
8
9

10 DISCUSSION 11

12
13
14
15 Age as well as several life style factors have been reported to be potential risk factors for
16
17 OAB (see introduction). While female gender has not been established as a risk factor for
18
19 OAB, the majority of patients receiving OAB treatment are female (7, 8). Limited clinical
20
21 data have explored the effects of age and gender on treatment responses in OAB patients (7,
22
23 24), but the potential effects of life-style factors have not been reported to our knowledge.
24
25
26
27
28

29 Critique of methods 30

31
32
33
34 Our analysis is based upon an observational, large-scale, open-label study on the efficacy and
35
36 tolerability of darifenacin in routine clinical use. In the absence of a placebo group,
37
38 observational data do not allow for absolute conclusions about the safety and efficacy of
39
40 darifenacin. However, multiple placebo-controlled studies have already demonstrated the
41
42 absolute efficacy and tolerability of darifenacin (25-27). On the other hand, observational
43
44 studies have proven useful for comparisons of relative efficacy and tolerability between
45
46 patient groups of OAB patients (7, 8, 24). An observational study from routine clinical use
47
48 may be particularly advantageous to explore the roles of potential OAB risk factors in
49
50 treatment responses, because the strict inclusion and exclusion criteria of randomized
51
52 controlled studies may limit variability of these factors in the study population, particularly
53
54 for life style factors. Moreover, the expected inter-relatedness of several risk factors, e.g. of
55
56 smoking and alcohol use, requires large patient numbers to yield the necessary statistical
57
58
59
60

1
2
3 power for detection of minor effects. Such large patient numbers are easier to collect from
4
5 observational studies.
6
7
8
9

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.
12
13 For example, the quantitative assessment of life style factors is everything but straightforward,
14
15 particularly when it comes to factors such as alcohol consumption where many patients may
16
17 provide somewhat “beautified” responses. Given the practical limitations of a large and non-
18
19 interventional study we had chosen for an assessment graded by the physician into 3-4
20
21 categories. While this may be suboptimal for a dedicated study into e.g. alcohol consumption,
22
23 it reflects a necessary compromise between the scientifically desirable and the practically
24
25 feasible. Finally, we have also used physician ratings of global efficacy and tolerability, as
26
27 particularly the latter has proven to yield a statistically sensitive means to pick up differences
28
29 in tolerability despite a typically reported incidence of adverse events in observational studies
30
31 in OAB (7, 8). These specific advantages and limitations should be kept in mind in the
32
33 interpretation of our data.
34
35
36
37
38
39
40
41
42

43 Treatment results

44
45
46
47
48 Age not only is a well-established risk factor for OAB (2-4) but is also known to affect the
49
50 expression of muscarinic receptors in the bladder and other tissues including salivary glands
51
52 and heart (23, 30). Until now only limited data on the effects of age on treatment results in
53
54 OAB patients had been reported: One large observational study with tolterodine demonstrated
55
56 a statistically significant but probably clinically irrelevant adverse effect of age on treatment-
57
58 associated symptom improvement and global efficacy (7). On the other hand, this small
59
60

1
2
3 negative effect was compensated by increasing severity of baseline symptoms with age and
4
5 the strong statistical effect of baseline symptoms on the overall improvement. The present
6
7 data for darifenacin also report a statistically significant but very small negative effect of age
8
9 on treatment-associated improvements of OAB symptoms and global efficacy. This may even
10
11 be somewhat under-estimated due to a trend for a higher dose with increasing age. While age
12
13 did not significantly affect the global tolerability of tolterodine (7), it was shown to have a
14
15 statistically significant but very small adverse effect on the tolerability of solifenacin (8).
16
17 Very similar findings were obtained in the present study with darifenacin. Therefore, the
18
19 overall data show that muscarinic receptor antagonists have similar efficacy across all age
20
21 groups. The overall tolerability may decline with increasing age, but this may reflect the
22
23 overall health status of the elderly rather than specific treatment-related adverse effects.
24
25
26
27
28
29
30
31

32 Although women receive muscarinic antagonist treatment of OAB symptoms more frequently
33
34 than men, the prevalence of OAB does not exhibit major gender differences (2-4) and
35
36 muscarinic receptor expression in the bladder is similar in both genders across multiple
37
38 species (23). An observational study with tolterodine has reported that gender may have
39
40 statistically significant effects on therapeutic efficacy, which are very small and not seen for
41
42 all OAB symptoms; moreover, gender did not significantly affect the tolerability of
43
44 tolterodine (7). Gender did not affect the efficacy or tolerability of solifenacin in a similar
45
46 study (24). In line with these observations, the present study found very similar effects in both
47
48 genders upon treatment with darifenacin. Therefore, it appears that muscarinic antagonists as
49
50 a class are similarly effective and tolerated in male and female OAB patients.
51
52
53
54
55
56

57 The major novel aspect of the present analysis was the exploration of potential effects of life
58
59 style factors on the efficacy and tolerability of a muscarinic antagonist in the treatment of
60

1
2
3 OAB. While a high BMI has been demonstrated as a risk factor for OAB (see introduction),
4
5 our data demonstrate that it does not affect the efficacy or tolerability of darifenacin in a
6
7 clinically relevant manner. This is interesting as obesity and treatment response could not
8
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
12
13 greater likelihood for a higher darifenacin dose in the present study. While the role of alcohol,
14
15 smoking and caffeine intake as risk factors for OAB remains under debate (see introduction),
16
17 neither affected the efficacy or tolerability of darifenacin in the present study, although a trend
18
19 for a higher darifenacin dose with greater alcohol (but not smoking or coffee) consumption
20
21 may have masked an effect of alcohol on treatment.
22
23
24
25
26
27
28

29 CONCLUSION

30
31
32
33
34 In conclusion, the available data show that age, gender and several life style factors have no
35
36 clinically relevant impact on the efficacy or tolerability of the muscarinic receptor antagonist
37
38 darifenacin. Thus, muscarinic receptor antagonists can be expected to be similarly effective
39
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
45
46 life style advice.
47
48
49
50
51
52

53 Acknowledgements: Bayer Vital had funded the underlying study as well as the present
54
55 analyses.
56
57
58
59
60

REFERENCES

- 1 Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, *et al.* The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; **21**: 167-178.
- 2 Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff JW, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001; **87**: 760-766.
- 3 Stewart WF, van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, *et al.* Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003; **20**: 327-336.
- 4 Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, *et al.* Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol* 2006; **50**: 1306-1315.
- 5 Michel MC, Chapple CR. Basic mechanisms of urgency: basic and clinical evidence. *Eur Urol* 2009; **56**: 298-308.
- 6 Goepel M, Hoffmann J, Piro M, Rübber H, Michel MC. Prevalence and physician awareness of symptoms of urinary bladder dysfunction. *Eur Urol* 2002; **41**: 234-239.
- 7 Michel MC, Schneider T, Kregge S, Goepel M. Do gender or age affect the efficacy and safety of tolterodine? *J Urol* 2002; **168**: 1027-1031.

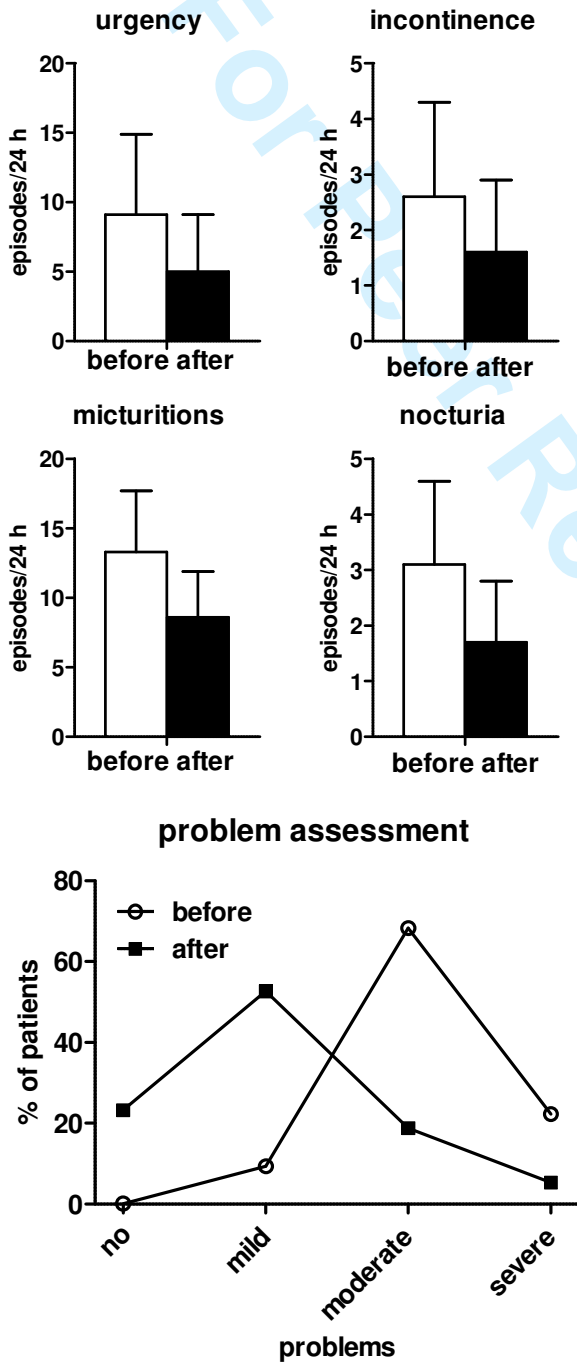
- 1
2
3 8 Michel MC, Wetterauer U, Vogel M, de la Rosette JJMCH. Cardiovascular safety and
4 overall tolerability of solifenacin in routine clinical use. *Drug Safety* 2008; **31**: 505-
5
6 514.
7
8
9
10
11 9 Brown JS, Seeley DG, Fong J, Black DM, Ensrud KE, Grady D. Urinary incontinence
12 in older women: who is at risk? *Obstet Gynecol* 1996; **87**: 715-721.
13
14
15
16
17 10 Espino DV, Palmer RF, Miles TP, Mouton CP, Lichtenstein MJ, Markides KP.
18 Prevalence and severity of urinary incontinence in elderly Mexican-American women.
19
20 *J Am Geriatr Soc* 2003; **51**: 1580-1586.
21
22
23
24
25 11 Hannestad YS, Rortveit G, Daltveit AK, Hunskaar S. Are smoking and other lifestyle
26 factors associated with female urinary incontinence? The Norwegian EPINCONT
27
28 study. *BJOG* 2003; **110**: 247-254.
29
30
31
32
33 12 Melville JL, Katon W, Delaney K, Newton K. Urinary incontinence in US women. A
34 population-based study. *Arch Intern Med* 2005; **165**: 537-542.
35
36
37
38
39 13 Dallosso HM, McGrother CW, Matthews RJ, Donaldson MMK. The association of
40 diet and other lifestyle factors with overactive bladder and stress incontinence: a
41
42 longitudinal study in women. *BJU Int* 2003; **92**: 69-77.
43
44
45
46
47 14 Arya LA, Myers DL, Jackson ND. Dietary caffeine intake and the risk for detrusor
48 instability: a case-control study. *Obstet Gynecol* 2000; **96**: 85-89.
49
50
51
52
53 15 Shiri R, Hakama M, Häkkinen J, Auvinen A, Huhtala H, Tammela TLJ, *et al.* The
54 effects of lifestyle factors on the incidence of nocturia. *J Urol* 2008; **180**: 2059-2062.
55
56
57
58
59
60

- 1
2
3 16 Brown JS, Grady D, Ouslander JG, Herzog AR, Varner E, Posner SF. Prevalence of
4 urinary incontinence and associated risk factors in postmenopausal women. *Obstet*
5
6 *Gynecol* 1999; **94**: 66-70.
7
8
9
10
11 17 Dallosso HM, Matthews RJ, McGrother CW, Donaldson MMK, Shaw C. The
12 association of diet and other lifestyle factors with the onset of overactive bladder: a
13 longitudinal study in men. *Public Health Nutr* 2004; **7**: 885-891.
14
15
16
17
18
19 18 Wyman JF, Burgio KL, Newman DK. Practical aspects of lifestyle modifications and
20 behavioural interventions in the treatment of overactive bladder and urgency urinary
21 incontinence. *Int J Clin Pract* 2009; **63**: 1177-1191.
22
23
24
25
26
27
28 19 Hashim H, Abrams P. How should patients with an overactive bladder manipulate
29 their fluid intake? *BJU Int* 2008; **102**: 62-66.
30
31
32
33 20 Natarajan V, Master V, Ogan K. Effects of obesity and weight loss in patients with
34 nononcological urological disease. *J Urol* 2009; **181**: 2424-2429.
35
36
37
38
39 21 Chapple CR, Khullar V, Gabriel Z, Muston D, Biton CE, Weinstein D. The effects of
40 antimuscarinic treatments in overactive bladder: an update of a systematic review and
41 meta-analysis. *Eur Urol* 2008; **54**: 543-562.
42
43
44
45
46
47 22 Novara G, Galfano A, Secco S, D'Elia C, Cavalleri S, Ficarra V, *et al.* A systematic
48 review and meta-analysis of randomized controlled trials with antimuscarinic drugs
49 for overactive bladder. *Eur Urol* 2008; **54**: 740-764.
50
51
52
53
54
55 23 Michel MC, Barendrecht MM. Physiological and pathological regulation of the
56 autonomic control of urinary bladder contractility. *Pharmacol Ther* 2008; **117**: 297-
57 312.
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- 24 Witte LPW, Peschers U, Vogel M, de la Rosette JJMCH, Michel MC. Does the number of previous vaginal deliveries affect overactive bladder symptoms or their response to treatment? *LUTS* 2009; **1**: 82-87.
- 25 Chapple C, Steers W, Norton P, Millard R, Kralidis G, Glavind K, *et al.* A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M₃ selective receptor antagonist, in the treatment of overactive bladder. *BJU Int* 2005; **95**: 993-1001.
- 26 Foote J, Glavind K, Kralidis G, Wyndaele J-J. Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of darifenacin, an M₃ selective receptor antagonist. *Eur Urol* 2005; **48**: 471-477.
- 27 Michel MC, Oelke M, Zinner N. Novel muscarinic antagonists to treat incontinence and/or overactive bladder. *Drug Discov Today: Ther Strat* 2005; **2**: 1-6.
- 28 Michel MC, Oelke M, Goepel M, Beck E, Burkart M. Relationships among symptoms, bother, and treatment satisfaction in overactive bladder patients. *Neurourol Urodyn* 2007; **26**: 190-195.
- 29 Michel MC, de la Rosette JJMCH, Piro M, Schneider T. Comparison of symptom severity and treatment response in patients with incontinent and continent overactive bladder. *Eur Urol* 2005; **48**: 110-115.
- 30 Brodde O-E, Michel MC. Adrenergic and muscarinic receptors in the human heart. *Pharmacol Rev* 1999; **51**: 651-689.

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		
Age, per year	0.0127 \pm 0.0045	0.0049
Gender, relative to male	-0.4416 \pm 0.1379	0.0014
BMI, per kg/m²	0.0298 \pm 0.0146	0.0421
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		
Age, per year	0.0047 \pm 0.0020	0.0210
Gender, relative to male	-0.0011 \pm 0.0659	0.9863
BMI, per kg/m ²	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 ± 0.0586	0.6562
Moderate to severe alcohol, relative to none	0.0803 ± 0.0903	0.3739
Moderate caffeine, relative to none	-0.1041 ± 0.0773	0.1779
Severe caffeine, relative to none	0.1131 ± 0.1203	0.3470
Baseline incontinence, per episode	0.3948 ± 0.0133	<0.0001
Micturition episode improvement		
Age, per year	0.0190 ± 0.0042	<0.0001
Gender, relative to male	-0.3316 ± 0.1247	0.0079
BMI, per kg/m ²	0.0219 ± 0.0134	0.1012
Previous smoking, relative to none	0.0224 ± 0.1897	0.9060
Current smoking, relative to none	0.1535 ± 0.1445	0.2880
Mild alcohol, relative to none	-0.1047 ± 0.1215	0.3889
Moderate to severe alcohol, relative to none	0.0744 ± 0.1842	0.6861
Moderate caffeine, relative to none	-0.2001 ± 0.1597	0.2104
Severe caffeine, relative to none	0.2477 ± 0.2430	0.3081
Baseline micturitions, per episode	0.4623 ± 0.0115	<0.0001
Nocturia episode improvement		
Age, per year	0.0097 ± 0.0014	<0.0001
Gender, relative to male	-0.1638 ± 0.0423	0.0001
BMI, per kg/m ²	0.0085 ± 0.0045	0.0608
Previous smoking, relative to none	-0.0317 ± 0.0645	0.6231
Current smoking, relative to none	0.0897 ± 0.0491	0.0677
Mild alcohol, relative to none	-0.0693 ± 0.04121	0.0927
Moderate to severe alcohol, relative to none	-0.0659 ± 0.0626	0.2925

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

For Peer Review Only

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	0.981 (0.975; 0.988)	0.978 (0.970; 0.985)	0.982 (0.971; 0.993)
Gender, relative to male	1.313 (1.087; 1.587)	1.396 (1.135; 1.716)	1.047 (0.746; 1.471)
BMI, per kg/m ²	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)

For Peer Review Only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

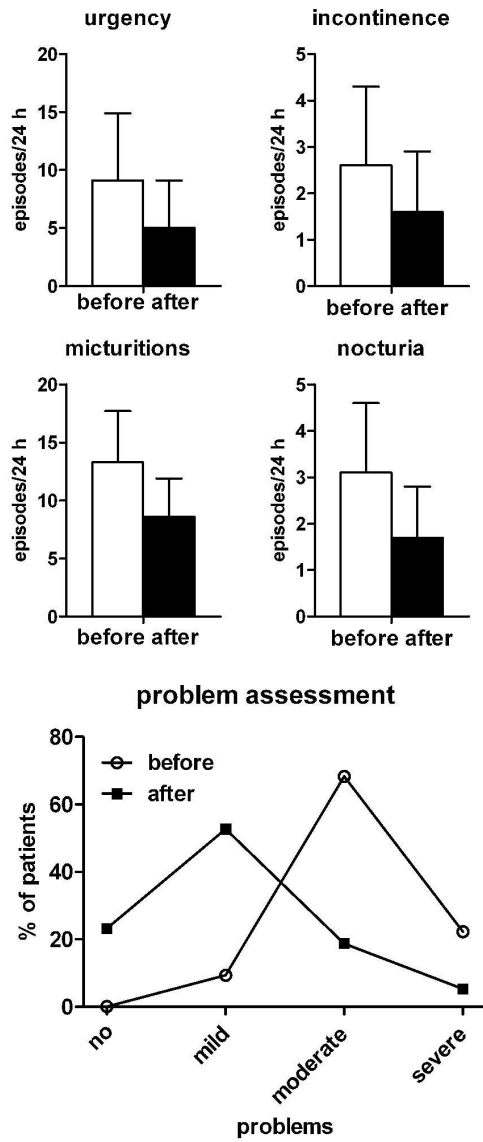


Figure 1
120x267mm (600 x 600 DPI)