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How are women with SUI-symptoms treated with duloxetine in real life practice? - Preliminary results from a large observational study in Germany

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How are women with SUI-symptoms treated with duloxetine in real life practice? - Preliminary results from a large observational study in Germany

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3 **How are women with SUI-symptoms treated with duloxetine in real life practice? -**

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6 **Preliminary results from a large observational study in Germany**

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56 Advisory Board.

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Abstract

Background: Duloxetine was found safe and effective in the treatment of moderate to severe female stress urinary incontinence (SUI) in controlled clinical trials; complementary data from routine clinical practice are still wanted.

Objectives: To explore use of various initial duloxetine doses by physicians in the treatment of female SUI in routine clinical practice and its implications on drug safety and patients' subjective impression of effectiveness.

Methods: Adult women treated with duloxetine for SUI symptoms were documented as part of an ongoing large-scale observational study in Germany. Data collected at baseline, after 4 and after 12 weeks were evaluated by initial doses. Statistics were descriptive, 95% confidence intervals were calculated for adverse event (AE) rates.

Results: 7,888 adult women were treated with duloxetine; their mean age was 61.4 years, BMI 27 kg/m², incontinence episode frequency (IEF) 14.0/week. Previous SUI treatments were observed in 52.2%, comorbidities in 60.4% of the patients. 90.7% reported reduced frequency of SUI-episodes, 12.1 % any AE; nausea (5.7%) and vertigo (1.6%) were reported most frequently. 52.2% of patients were initiated on a duloxetine dose of 40 mg /day. Only minor differences in patient characteristics, effectiveness and tolerability were associated with varying initial duloxetine doses.

Conclusions: Many women received lower duloxetine doses than expected based on evidence-based dosing recommendations. Though SUI patients in this study had a higher health risk because of old age and multiple comorbidities than in previous

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controlled clinical trials, AE rates were lower, possibly due to the observational character of the study and/or the use of rather low doses. Similar AE rates for varying initial doses possibly reflect sensible dose-adjustment to individual needs.

For Peer Review Only

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3 **What's known:**
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7 Duloxetine was found safe and effective in the treatment of moderate to severe female
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9 stress urinary incontinence in controlled clinical trials. Up-titration over the first two
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11 weeks of treatment increases the tolerability of duloxetine in the treatment of stress
12
13 urinary incontinence.
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17 **What's new:**
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21 The female SUI-patients documented in this German observational study had a higher
22
23 mean age than patients in controlled clinical trials and a high rate of comorbidities.
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25 Primary care physicians and specialists choose very low duloxetine doses for a high
26
27 proportion of patients. AE-Rates were similar for varying initial doses and generally
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29 lower than reported in controlled clinical trials.
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Introduction

Urinary incontinence, defined by the International Continence Society (ICS) as "the complaint of any involuntary leakage of urine", is associated with substantial impairment of quality of life and a considerable financial burden to the patients and the health care systems (1, 2, 3). The risk of developing urinary incontinence increases with age and its prevalence is higher in women than in men (3, 4). Stress Urinary Incontinence (SUI), the involuntary leakage of urine on effort, exertion, sneezing or coughing (1), accounts for approximately half of all urinary incontinence cases experienced by adult women (4; 2, 3, 5, 6).

Duloxetine is the first medication approved in Europe for the treatment of moderate to severe SUI symptoms. Trials in cats (7, 8, 9) and healthy female volunteers (10) suggested that the selective serotonin-norepinephrine reuptake inhibitor duloxetine enhances the excitability of the pudendal motor neurons and the urethral sphincter contractility, and suppresses bladder activity.

Safety data obtained from controlled clinical trials in women with SUI (11, 12, 13, 14, 15) largely report the most common adverse reactions associated with duloxetine (e.g. nausea, dry mouth, and insomnia). Less common adverse drug reactions may escape observation due to limited sample sizes. Furthermore, due to restrictive in- and exclusion criteria, patients included in controlled clinical trials hardly reflect the typical characteristics and specific health risks of patients, who receive duloxetine for the treatment of SUI in real life. To explore these issues, DUROSA ("**D**uloxetine **R**outine **S**afety") was set up as a non-interventional, large scale, post-authorization safety study

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3 in February 2005, shortly after the approval of duloxetine for the treatment of SUI in
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6 Germany.

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9 Only a few months later, findings from a randomized study (16) suggested that patients
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11 might profit in respect of tolerability if they were initiated with reduced doses of
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13 duloxetine and gradually up-titrated to the recommended dose of 80 mg/day. Dosage
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15 recommendations were adjusted accordingly in the Summary of Product
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17 Characteristics. As a consequence, we perceived a demand for data on the handling of
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19 initial dosage and up-titration from the physicians in clinical practice. Without having
20
21 planned a preliminary evaluation considering this objective, we found that the interim
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23 safety reports, which were done regularly for this post authorization safety study, did
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26 provide sufficient data to give an insight into up-titration in everyday clinical practice and
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29 its results, and decided that these should not be withheld.
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32 33 34 35 **Methods**

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38 The primary objective of the overall DUROSA study was to evaluate the safety of
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40 duloxetine in the treatment of women with symptoms of moderate to severe SUI in a
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42 routine clinical setting in Germany. Further objectives addressed in this study were the
43
44 characterisation of the patient population who receive duloxetine SUI treatment under
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46 routine prescribing conditions in Germany, physicians' dosing behaviour, and the
47
48 patients' self-estimation of treatment effectiveness. According to the European
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50 Pharmacovigilance guidelines for post authorisation safety studies, brief progress
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52 reports were drawn every six months. The data presented in this paper were derived
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55 from the safety report of January 2008.
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3 DUROSA was designed as an open-label, prospective, non-interventional, post-
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5 authorisation safety study. Data were collected in the course of routine clinical practice
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7 by mostly office-based urologists, gynaecologists and general practitioners throughout
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9
10 Germany. Eligible for documentation were women aged ≥ 18 years, who received
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12 treatment for SUI symptoms. Patients could be treated with duloxetine (data reported
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14 here), pelvic floor muscle training (PFMT), pessaries, or any other conservative
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16 treatment option, but no surgical therapy was to be considered within the duration of the
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18 study. The choice of treatment was entirely at the discretion of the physician. Adjunct
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20 and combination therapy was acceptable for all patient groups.
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26 Assuming a sample size of 8,000 duloxetine patients, an uncommon adverse drug
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28 reaction with an incidence of 1% is likely to be observed in at least 65 patients with a
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30 probability of 0.95. Thus, with the present sample of 7,888 duloxetine patients, at least
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32 64 patients with an adverse drug reaction that has an incidence of 1% can be expected
33
34 to be documented with a probability of 0.95.
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39 Documentation started with the patient's initiation on a new treatment for SUI (baseline).
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41 Further documentation of SUI treatment and of treatment outcomes including adverse
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43 events (AE) was scheduled 4 and 12 weeks after baseline. On request of the EMEA, an
44
45 additional 24-week follow-up was introduced as an addendum to the original study
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47 protocol, together with a modified set of documentation forms (DCF-24). This
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49 amendment applied to patients from primary health care physicians only, who could
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51 routinely observe their patients over such a long period. Patients from urologist and
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53 gynaecologist practices finished the study with a closing documentation following the
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55 12-weeks scheme (DCF-12). Discontinuation rates therefore needed to be reported
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3 separately for patients following the DCF-12 or DCF-24 scheme. Apart from that, for
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5 reasons of comparability, we report data on AEs and effectiveness for the entire sample
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7 as collected until Visit 3 (week 12). The respective results from the 24-week
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9 observational period as well as those for patients on reference therapy (any other non-
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separately for patients following the DCF-12 or DCF-24 scheme. Apart from that, for reasons of comparability, we report data on AEs and effectiveness for the entire sample as collected until Visit 3 (week 12). The respective results from the 24-week observational period as well as those for patients on reference therapy (any other non-invasive SUI treatment) are not dealt with in this paper and will be published elsewhere.

For analysis, patients treated with duloxetine were assigned to evaluation cohorts by initial total daily duloxetine doses as follows: duloxetine initial dose of 20 mg/day (Dulox-20), duloxetine initial dose of 40 mg/day (Dulox-40) and duloxetine initial dose of 80 mg/day (Dulox-80), "other" initial doses and duloxetine overall (Dulox-all). The analysis was largely descriptive. For quantitative variables (e.g. age) arithmetic means, medians, standard deviations, minimum and maximum values, quartiles as well as the respective available sample size and the number of missing values per category were calculated. Qualitative variables were described using absolute and relative frequencies (adjusted relative frequencies where appropriate). To assess the rates of AEs in the overall duloxetine sample, we evaluated all AEs of DCF-12 patients and of DCF-24-patients with an onset date within 84 days (12 weeks) of Visit 1. Two sided 95% confidence intervals (CI) were calculated for the rates of AEs and serious adverse events (SAEs).

At baseline the following data were collected: patients' age, height, weight, number and type of deliveries, duration of SUI symptoms, incontinence episode frequency per week (IEF), number of pads used per week, previous treatment of SUI, whether the patient was pre- or post-menopausal and the physician's specialisation.

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3 Relevant concomitant diseases were documented, to allow for further assessment of
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5 possible causality of treatment emergent AEs. AEs were solicited by general
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7 questioning at all post-baseline visits, including start and stop dates as well as the
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9 investigator's assessment of causality, and coded according to the Medical Dictionary
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11 for Regulatory Activities (MedDRA).
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16 Objective assessments of efficacy would have interfered with the observational
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18 character of study, particularly in patients treated by general practitioners. Therefore the
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20 general satisfaction with current treatment and changes in incontinence episode
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22 frequency as subjectively perceived by the patients were assessed at every visit after
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24 baseline. Early discontinuations were reported, including the reasons. The initial daily
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26 dose of duloxetine was documented at baseline. Duloxetine dosage was reassessed at
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28 every following visit, documenting any change.
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34 DUROSA was conducted according to the ethical principles of the Declaration of
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36 Helsinki and approved by the ethic committee of the Georg-August University
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38 Goettingen, Germany. The patients provided written consent to the collection and
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40 release of anonymised data regarding treatment and its outcomes. Regulatory
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42 authorities were notified of this observational study according to the respective local
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44 requirements.
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50 **Results**

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54 At the date of the present evaluation (data lock 25 January 2008), 13,357 patients were
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56 enrolled; 7,888 of these had received duloxetine treatment and had a closing
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3 documentation (i.e. either finished the study or documented early discontinuation). All
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5 further data described in this paper are based on this sample.
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9 4,564 (57.9%) patients were documented following the original protocol of 12 weeks on
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11 DCF-12, 3,324 (42.1%) patients were recorded on DCF-24 according to the addendum.
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14 Due to the different schedule, early discontinuation rates of DCF-12 patients and
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16 DCF-24 patients were not comparable and therefore calculated separately:
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19 504 (11.0%) patients from the DCF-12-set and 203 (6.1%) from the DCF-24 set
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21 discontinued early; 171 (3.7%) patients from the DCF-12 set and 78 (2.3%) from the
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23 DCF-24 set reported an AE as reason for discontinuation. Other frequent reasons were:
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26 withdrawal of consent (1.1% / 0.7%), switch to surgical treatment (1.2% / 0.2%), and
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28 termination of SUI-therapy (0.8% / 0.6%), for DCF-12 and DCF-24 set, respectively.
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31 Details on the rates and reasons for early discontinuation are given in Table 1.
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34 More than half of the duloxetine patients were initiated with doses of 40 mg/day (4,121;
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36 52.2%), 2,193 (27.8%) started on 20 mg/day and 1,515 (19.2%) on 80 mg/day. Other
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39 initial doses were given to 59 (0.7%) of the patients. Because of the comparatively
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41 small size, this group was not considered further.
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45 The initial dosage cohorts were similar with respect to age, BMI and parity (Table 2).
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47 Age ranged between 20 and 96 years. More than half of the patients from all groups
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49 were aged 60 years and older (Dulox-all mean \pm SD 61.4 \pm 12.6, median 62);
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52 approximately one quarter were aged over 70 (75%-quartile Dulox-all: 70 years). The
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54 percentages of post-menopausal patients were: Dulox-20: 82%, Dulox-40: 81%, and
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57 Dulox-80: 80%. The mean BMI [kg/m²] ranged between 27.0 \pm 4.2 (Dulox-40) and 27.3
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3 ± 4.3 (Dulox-80). Corresponding BMI-medians of 26 and 27 [kg/m²] indicated overweight
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5 of some degree in more than half of the duloxetine patients. The mean number of child
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7 deliveries was 2.0 ± 1.2 in all initial dosage groups; approximately 10% of the reported
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9 deliveries were Caesarean sections.
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14 Mean previous SUI history for Dulox-all was 45.1 ± 56.0 months with a median of 27
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16 months; patients from the Dulox-80 group had suffered from previous SUI somewhat
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18 longer than Dulox-20 and Dulox-40 patients (median: 31, 25 and 26 months
19
20 respectively - see overview on baseline data in Table 2). With a median of 10
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22 incontinence episodes per week, less than half of the patients in this naturalistic setting
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24 met the criterion of moderate to severe SUI, which was defined as a frequency of ≥ 14
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26 SUI episodes per week in earlier controlled clinical trials (11, 12, 13, 14, 15). No
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28 relevant difference between the initial dosage groups was observed regarding numbers
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30 of incontinence episodes and pads used per week.
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37 Previous treatment for SUI had been received by more than half of the patients (Dulox-
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39 all 4116; 52.2%, see Table 3). Local hormones and PFMT were the most frequent
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41 forms of pre-treatment in all cohorts. Surgical procedures for SUI treatment had already
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43 been performed in 558 (7.1%) of all duloxetine patients. The procedures most
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45 frequently applied were anterior colporrhaphy, Burch colposuspension, tension free
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47 vaginal tapes and the Marshall-Marchetti-Krantz-procedure.
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52 Pre-existing concomitant diseases were found in 4764 (60.4 %) of the duloxetine
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54 patients; the rates for the initial dose cohorts were all about the same. Overall, the most
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3 frequent comorbidities were hypertension, lipid metabolism disorder and diabetes
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6 (Table 4).
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9 Overall, 3121 (39.6%) of the duloxetine-patients had seen an urologist, 3126 (39.6%)
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11 came from general practitioner practices; 1118 (14.2%) were treated by a
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13 gynaecologist, while from 523 (6.6%) of the patients the physician's specification was
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16 not available.
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20 Physicians of all specialities preferentially initiated their patients on 40/mg
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22 duloxetine/day. However, urologists rather tended to choose higher initial doses (Dulox-
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24 40 / Dulox-80: 56.5% / 20.4% vs. gynaecologists 48.8% / 12.3% and general
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26
27 practitioners 49.8% / 20.1%), while gynaecologists more often initiated their patients on
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29 the low dose of 20 mg/day (37.5% vs. urologist 22.8% and general practitioners 29.3%).
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33 As Figure 1 shows, 56.0% of the Dulox-20 patients were taking their initial doses at
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35 Week 12, while about 40% had been up-titrated (Week 12: 32.0% 40 mg/day, 8.4% 80
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37 mg/day). Of the Dulox-40 patients 52.2% received the initial dose at Week 12, 41.3%
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39 had been up-titrated, while the rate of patients who received reduced doses was 2.7 %.
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41
42 Almost 89% of the Dulox-80 patients were on the initial dose at Week 12; the dose was
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44 reduced to 40 mg/day in 8.2% and to 20 mg/day in 0.2% of the patients.
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49 A visible decrease in the relative frequency of urine leakages from baseline over the
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51 course of the study as reported by the patients was observed in all initial dose cohorts.
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53 At Week 12, 26.9% of the duloxetine patients reported no SUI episodes, while only
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55 9.3% reported unchanged or worsening SUI symptoms. The relative decrease in the
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3 frequency of SUI-episodes was similar for all initial dose cohorts. Details are given in
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6 Figure 2.

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9 The patients' satisfaction with duloxetine therapy increased over time (Week 4: 20.7
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11 very satisfied, 51.6% satisfied, Week 12: 40.4% and 48.3% respectively). For the
12
13 details on patient satisfaction see Figure 3.

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18 AE-rates were higher for Dulox-80 (14.1%, CI 12.4 to 16.0) than for Dulox-20 (11.7%,
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20 CI 10.4 to 13.1) and Dulox-40 (11.6%, CI 10.6 to 12.6; see Table 5). Overall, the most
21
22 common AEs were nausea (5.7%), vertigo (1.6%), dry mouth (1.2%) and fatigue
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24 (1.2%). AEs occurring in $\geq 0.5\%$ of patients are listed in Table 6. In 4.6% of all patients,
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26
27 an AE was associated with early discontinuation.

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31 SAEs were reported in 16 patients (0.2%). In 6 (<0.1%) patients SAEs were classified
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33 as possibly related to duloxetine by the investigator (1 nausea and anorexia, 1 gastritis,
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35 1 acute abdomen, subileus and urinary retention, 1 palpitation, sweating and peripheral
36
37 oedema, 1 vertigo and speech impairment and 1 confusional state plus dermatozoon
38
39 delusion). Three SAEs with lethal outcome occurred in patients on duloxetine within 12
40
41 weeks of treatment: 1 natural death, 1 acute cardiac failure (age 81 and 86,
42
43 respectively) and 1 road traffic accident. None of these fatalities was judged as therapy
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45 related.

46 47 48 49 50 **Discussion**

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54 Including 7,888 women with SUI symptoms, these interim data from the DUROSA study
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57 are providing a preliminary survey on the use of duloxetine in SUI-treatment under
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3 routine conditions in Germany, with special regard to the characteristics of the typical
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5 female SUI-patient population, as well as physicians' dosing habits in relation to
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7 tolerability and effectiveness.
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11 Randomised clinical trials investigating duloxetine in the treatment of women with
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13 symptoms of SUI were mostly conducted with the recommended target dose of 80
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15 mg/day (2 x 40 mg; 11, 12, 13, 14, 15).
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20 The present findings from the DUROSA-study showed that under real life conditions
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22 more than 80% of the patients were actually initiated with daily doses of less than
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24 80 mg, which is in line with the current recommendation of up-titration. However, these
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26 low starting doses apparently were not up-titrated to the recommended target dose of
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28 80 mg/day in more than half of these patients during the observational period of 12
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30 weeks.
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35 Especially gynaecologists were observed to choose doses even more cautiously than
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37 other physician groups. It should be noted, however, that in DUROSA urologists' sites
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39 were initiated first, and gynaecologists started patient enrolment several weeks later.
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41 Concurrently, findings from a randomised placebo controlled trial suggested that some
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43 patients might profit from receiving lower duloxetine doses of 40 mg/day (2 x 20 mg) for
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45 the first two weeks, suffering less from nausea or dizziness, which again led to lower
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47 rates of discontinuation due to AEs compared to patients who started at a full dose of
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49 80 mg/day. The presentation of these finding at the ICS in Montreal (17) might already
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51 have influenced the physicians' dosing decisions. Shortly afterwards, the data were
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3 published in a full paper by Castro-Diaz (16) and eventually caused a respective
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5 change in dosing recommendations, but only after DUROSA had already been started.
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9 It is therefore even more remarkable how cautiously physicians of all specialties were
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11 adjusting doses from the very beginning, possibly reflecting the physicians' attention to
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13 the perceived individual health risk of the respective patient.
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17 The majority of the patients initiated on 20 or 40 mg/day were content with the
18
19 effectiveness of their treatment at Week 12 of the observational period, though more
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21 than half of them had not been up-titrated. Treatment satisfaction at Week 12 was
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23 comparably high in all initial dosing cohorts ("very satisfied" or "satisfied": Dulox-20:
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25 88.2%, Dulox-40: 88.4%, Dulox-80: 89.9%).
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29 It might be assumed that patients with less severe SUI symptoms or fewer known risk
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31 factors for SUI were started with lower duloxetine dosages, but the results from
32
33 DUROSA show no relevant differences between the initial dosage cohorts in terms of
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35 mean age, BMI, number of deliveries, incontinence episode frequency and weekly pad
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37 usages; only a slightly longer history of SUI was associated with higher starting doses
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39 of duloxetine (mean duration of SUI 43.2 ± 51.9 and 43.5 ± 54.2 months in Dulox-20
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41 and Dulox-40 patients, respectively, but 51.8 ± 65.4 months in Dulox-80 patients).
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43 Norton et al. (14) also observed significant efficacy for both 40 and 80 mg/day
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45 duloxetine, however, their results for 20 mg/day did not significantly differ from placebo
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47 (p-values versus placebo for change of median IEF: Dulox-20: 0.6, Dulox-40: 0.02,
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49 Dulox-80: <0.001).
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3 Overall, more than 60% of the duloxetine patients reported concomitant diseases, with
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5 hypertension, lipid metabolism disorder, diabetes and cardiac disease being the most
6
7 common. A high rate of multimorbidity must be assumed from the numbers, indicating a
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9 substantial prevalence of metabolic syndrome.
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14 The rate of AEs found for duloxetine-patients in DUROSA was notably lower than rates
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16 reported from previous controlled registration studies (18), which report percentages for
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18 e.g. nausea (DUROSA 5.7%) between 22.7 (12) and 45.5 % (11, with doses up to 2x60
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20 mg/day). Norton (14) however, reported values which are more similar to those found in
21
22 DUROSA (nausea 13% for 80 mg over 12 weeks).
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27 Overall, the AEs observed under duloxetine treatment in this study did not differ
28
29 substantially from the known safety-profile of duloxetine in the treatment of SUI (19).
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31
32 Most AEs did not lead to early discontinuation, which correlates with the findings of
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34 Moore (20), who also reported that the most common adverse reactions to duloxetine,
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36 nausea, fatigue, and dry mouth, were mild to moderate, and did not lead to
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38 discontinuation as they were mostly transient.
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42 The initial doses showed less association with the frequency or pattern of AEs in this
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44 interim sample than expected regarding the results of Castro-Diaz (16). More than 40%
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46 of the patients starting with lower doses were up-titrated within the first weeks, and
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48 received doses of 40 or 80 mg/day for the further course of the study. This might have
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50 contributed to the small difference in AE-rates associated with the initial doses.
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54 Nevertheless, a considerable number of patients who started on 20 mg/day or
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56 40 mg/day apparently stayed on these doses over the whole course of the study, and
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3 so did more than 80% of those who started on 80 mg/day (Figure 1). The lack of
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6 relevant difference in AE-rates associated with the initial dosage possibly reflects that
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8 physicians choose lower initial doses for patients deemed more susceptible and
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10 adjusted them very carefully according to the patient's individual needs; such
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12 individualised dosing approaches are usually not allowed in the strict setting of
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14 controlled clinical trials.
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19 SAEs were rare, given the large case numbers. The AEs judged as therapy-related
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21 resembled those which had been described previously for duloxetine. None of the SAEs
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23 with lethal outcome were judged related to SUI-therapy, but rather associated with
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25 cardiovascular disease and old age and can be considered within the normal mortality
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27 rates for the observed age classes (21).
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32 As these interim data were not originally intended for publication, the analysis largely
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34 lacks indicators of significance. Comparisons of the results in the different initial dose
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36 cohorts can only be made descriptively here. More sophisticated modelling analyses
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38 allowing comparison of the dose cohorts adjusted for baseline differences between the
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40 cohorts in demographic and disease characteristics will be performed using the
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42 complete database and published at a later date. The frequency of SUI events was only
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44 assessed categorically, reflecting the patient's subjective impression, which might
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46 include the perception of a placebo effect. Results from this section therefore should be
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48 interpreted cautiously. Due to the observational character of this study, a considerable
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50 number of patients with rather mild SUI were included and treated with duloxetine.
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53 Earlier studies (14) have already reported that in such patients, the effects of duloxetine
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3 may mingle with a placebo effect of similar size and thus explain the good results for
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6 the lower daily doses of 20 and 40 mg/day duloxetine.
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9 **Conclusion**

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12 These data from a large observational study show that in routine clinical practice,
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15 physicians are confronted with patients who have a much higher health risk because of
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18 old age and multiple comorbidities than previously reported in controlled clinical trials.
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20 This might be one explanation why a considerable number of the physicians prescribed
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22 initial doses which were lower than recommended in the official scheme of up-titration
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25 described in the Summary of Product Characteristics. This cautious adjustment of
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27 dosing patterns to the particular needs of the individual SUI patient is also reflected by
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30 the comparatively low rate of AEs, though this might also be due to the observational
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32 design of the study. Despite the low doses, a surprising majority of these patients
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34 reported a considerable reduction of SUI episodes and general satisfaction with their
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37 therapy. Altogether, these findings underline the importance of observational research
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39 under naturalistic conditions, and confirm the safety and effectiveness of duloxetine in
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41 routine clinical practice.
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10

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17 Concept, design:
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20 Martina Manning, Andreas Gross, Hans D. Methfessel, Martin C. Michel, Ines Pages
21

22
23
24 Statistics:
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27 Deborah Quail
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31 Data analysis and interpretation:
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35 Martina Manning, Anette Minarzyk
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38 Drafting of article:
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42 Martina Manning, Anette Minarzyk, Ursula Gotsch
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45 Critical revision of article:
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49 Andreas Gross, Hans D. Methfessel, Martin C. Michel, Ines Pages, Deborah Quail
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56 Approval: All authors reviewed and approved the final version of the manuscript.
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For Peer Review Only

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3 **Tables:**
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6 Table 1 Early Discontinuations
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| | Patients with 12-week DCF | | Patients with 24-week DCF | |
|-------------------------------------|---------------------------|-------|---------------------------|-------|
| | n | % | n | % |
| 11 N | 4564 | 100.0 | 3324 | 100.0 |
| 12 Early discontinuation, overall | 504 | 11.0 | 203 | 6.1 |
| 13 Missing data | 37 | 0.8 | 34 | 1.0 |
| 14 | | | | |
| 15 Reasons for discontinuation*: | | | | |
| 16 | | | | |
| 17 Adverse events | 171 | 3.7 | 78 | 2.3 |
| 18 Other | 152 | 3.3 | 75 | 2.3 |
| 19 Surgical procedure (SUI-related) | 57 | 1.2 | 5 | 0.2 |
| 20 Patient withdrew consent | 49 | 1.1 | 22 | 0.7 |
| 21 SUI-therapy stopped | 37 | 0.8 | 19 | 0.6 |
| 22 Patient moved house | 25 | 0.5 | 5 | 0.2 |
| 23 Change of physician | 23 | 0.5 | 6 | 0.2 |
| 24 Lost to follow-up | 14 | 0.3 | 0 | 0.0 |
| 25 Patient died | 0 | 0.0 | 6 | 0.2 |

26 * multiple mentioning was possible
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Table 2 Patient Characteristics

| | | Dulox-all | Dulox-20 | Dulox-40 | Dulox-80 |
|------------------------------|--------|-----------|----------|----------|----------|
| AGE [years] | N | 7887 | 2192 | 4121 | 1515 |
| | Mean | 61.4 | 61.8 | 61.3 | 60.8 |
| | Median | 62 | 62 | 62 | 62 |
| | SD | 12.6 | 12.8 | 12.7 | 11.8 |
| BMI [kg/m ²] | N | 7873 | 2191 | 4109 | 1514 |
| | Mean | 27.1 | 27.1 | 27.0 | 27.3 |
| | Median | 27 | 26 | 26 | 27 |
| | SD | 4.3 | 4.6 | 4.2 | 4.3 |
| Number of child deliveries | N | 7828 | 2178 | 4082 | 1509 |
| | Mean | 2.0 | 2.0 | 2.0 | 2.0 |
| | Median | 2 | 2 | 2 | 2 |
| | SD | 1.2 | 1.2 | 1.2 | 1.2 |
| Duration of SUI [Months] | N | 7835 | 2176 | 4089 | 1511 |
| | Mean | 45.1 | 43.2 | 43.5 | 51.8 |
| | Median | 27 | 25 | 26 | 31 |
| | SD | 56.0 | 51.9 | 54.2 | 65.4 |
| IEF* per week | N | 7868 | 2186 | 4110 | 1513 |
| | Mean | 14.0 | 14.4 | 14.0 | 13.5 |
| | Median | 10 | 10 | 10 | 10 |
| | SD | 12.4 | 13.2 | 12.1 | 11.9 |
| Number of pads used per week | N | 7806 | 2167 | 4082 | 1503 |
| | Mean | 16.8 | 16.5 | 16.7 | 17.6 |
| | Median | 14 | 14 | 14 | 14 |
| | SD | 11.3 | 10.7 | 11.5 | 11.6 |

*incontinence episode frequency

Table 3 Type of Previous Treatment for SUI*

| | Dulox-all | | Dulox-20 | | Dulox-40 | | Dulox-80 | |
|------------------------------|-----------|------|----------|------|----------|------|----------|------|
| | N=7888 | | N=2193 | | N=4121 | | N=1515 | |
| | n | % | n | % | n | % | n | % |
| Any specification | 4116 | 52.2 | 1079 | 49.2 | 2242 | 54.4 | 757 | 50.0 |
| Pelvic floor muscle training | 2975 | 37.7 | 734 | 33.5 | 1628 | 39.5 | 585 | 38.6 |
| Hormones local | 1431 | 18.1 | 382 | 17.4 | 795 | 19.3 | 246 | 16.2 |
| Homeopathy | 524 | 6.6 | 152 | 6.9 | 282 | 6.8 | 87 | 5.7 |
| Other | 390 | 4.9 | 105 | 4.8 | 222 | 5.4 | 59 | 3.9 |
| Pessary | 258 | 3.3 | 61 | 2.8 | 145 | 3.5 | 49 | 3.2 |
| Surgical procedure | 558 | 7.1 | 156 | 7.1 | 297 | 7.2 | 99 | 6.5 |
| Anterior colporrhaphy | 224 | 2.8 | 69 | 3.1 | 111 | 2.7 | 42 | 2.8 |
| Burch colposuspension | 123 | 1.6 | 32 | 1.5 | 65 | 1.6 | 24 | 1.6 |
| Tension free vaginal tapes | 117 | 1.5 | 33 | 1.5 | 66 | 1.6 | 17 | 1.1 |
| Marshall-Marchetti-Krantz | 81 | 1.0 | 27 | 1.2 | 39 | 0.9 | 14 | 0.9 |
| Slings | 39 | 0.5 | 13 | 0.6 | 21 | 0.5 | 5 | 0.3 |
| Needle suspension | 15 | 0.2 | 4 | 0.2 | 10 | 0.2 | 1 | 0.1 |
| Injectables | 13 | 0.2 | 6 | 0.3 | 4 | 0.1 | 3 | 0.2 |
| Endoscopic colposuspension | 9 | 0.1 | 4 | 0.2 | 4 | 0.1 | 1 | 0.1 |
| Artificial sphincters | 4 | 0.1 | 0 | 0.0 | 3 | 0.1 | 1 | 0.1 |

* multiple mentioning was possible.

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Table 4 Comorbidities at Baseline*

| | Dulox-all N=7888 | | Dulox-20 N=2193 | | Dulox-40 N=4121 | | Dulox-80 N=1515 | |
|-------------------------------|---------------------|------|--------------------|------|--------------------|------|--------------------|------|
| | n | % | n | % | n | % | n | % |
| Any specification | 4764 | 60.4 | 1285 | 58.6 | 2526 | 61.3 | 919 | 60.7 |
| Hypertension | 3515 | 44.6 | 973 | 44.4 | 1840 | 44.6 | 677 | 44.7 |
| Lipid metabolism disorder | 1804 | 22.9 | 494 | 22.5 | 940 | 22.8 | 358 | 23.6 |
| Diabetes /Pre-Diabetes | 1506 | 19.1 | 387 | 17.6 | 827 | 20.1 | 281 | 18.5 |
| Heart diseases (| 779 | 9.9 | 235 | 10.7 | 407 | 9.9 | 130 | 8.6 |
| Depression | 737 | 9.3 | 252 | 11.5 | 355 | 8.6 | 124 | 8.2 |
| Bronchopulmonary diseases | 413 | 5.2 | 104 | 4.7 | 236 | 5.7 | 70 | 4.6 |
| Urinary hesitancy, neurogenic | 89 | 1.1 | 21 | 1.0 | 51 | 1.2 | 13 | 0.9 |
| Coagulation disorder | 78 | 1.0 | 19 | 0.9 | 42 | 1.0 | 16 | 1.1 |
| Liver diseases | 68 | 0.9 | 27 | 1.2 | 30 | 0.7 | 11 | 0.7 |
| Convulsions/seizures | 16 | 0.2 | 8 | 0.4 | 6 | 0.1 | 2 | 0.1 |
| Akathisia | 6 | 0.1 | 1 | 0.0 | 4 | 0.1 | 0 | 0.0 |

* multiple mentioning was possible

Table 5 Adverse Events (AEs) and Serious Adverse Events (SAEs) Occurring within 12 Weeks of Observation

| AEs | Dulox-all N=7888 | Dulox-20 N=2193 | Dulox-40 N=4121 | Dulox-80 N=1515 |
|--------------------------------|---------------------|--------------------|--------------------|--------------------|
| n | 957 | 257 | 477 | 214 |
| % | 12.1 | 11.7 | 11.6 | 14.1 |
| 95% Confidence Interval | 11.4 to 12.9 | 10.4 to 13.1 | 10.6 to 12.6 | 12.4 to 16.0 |
| Related AEs | | | | |
| n | 739 | 206 | 363 | 165 |
| % | 9.4 | 9.4 | 8.8 | 10.9 |
| 95% Confidence Interval | 8.7 to 10.0 | 8.2 to 10.7 | 8.0 to 9.7 | 9.4 to 12.6 |
| SAEs | | | | |
| n | 16 | 7 | 6 | 2 |
| % | 0.2 | 0.3 | 0.1 | 0.1 |
| 95% Confidence Interval | 0.1 to 0.3 | 0.1 to 0.7 | 0.1 to 0.3 | 0.0 to 0.5 |
| Related SAEs | | | | |
| n | 6 | 2 | 3 | 1 |
| % | <0.1 | <0.1 | <0.1 | <0.1 |
| 95% Confidence Interval | 0.0 to 0.2 | 0.0 to 0.3 | 0.0 to 0.2 | 0.0 to 0.4 |
| AEs leading to discontinuation | | | | |
| n | 363 | 117 | 175 | 67 |
| % | 4.6 | 5.3 | 4.2 | 4.4 |
| 95% Confidence Interval | 4.2 to 5.1 | 4.4 to 6.4 | 3.7 to 4.9 | 3.4 to 5.6 |
| AEs with lethal outcome | | | | |
| n | 3 | 1 | 2 | 0 |
| % | <0.1 | <0.1 | <0.1 | 0 |
| 95% Confidence Interval | 0.0 to 0.1 | 0.0 to 0.3 | 0.0 to 0.2 | - |

Table 6 Types of Adverse Events Occurring within 12 Weeks of Observation
in $\geq 0.5\%$ of Patients in any Duloxetine-Cohort (MedDRA Preferred Term)*

| Type of AE | Dulox-all | | Dulox-20 | | Dulox-40 | | Dulox-80. | |
|----------------|---------------|-----|---------------|-----|---------------|-----|---------------|-----|
| | N=7888 (100%) | | N=2193 (100%) | | N=4121 (100%) | | N=1515 (100%) | |
| | n | % | n | % | n | % | n | % |
| Nausea | 450 | 5.7 | 104 | 4.7 | 240 | 5.8 | 105 | 6.9 |
| Vertigo | 127 | 1.6 | 33 | 1.5 | 59 | 1.4 | 31 | 2.0 |
| Dry mouth | 94 | 1.2 | 27 | 1.2 | 49 | 1.2 | 18 | 1.2 |
| Fatigue | 92 | 1.2 | 19 | 0.9 | 43 | 1.0 | 30 | 2.0 |
| Headache | 82 | 1.0 | 21 | 1.0 | 42 | 1.0 | 19 | 1.3 |
| Constipation | 76 | 1.0 | 24 | 1.1 | 36 | 0.9 | 16 | 1.1 |
| Sleep disorder | 74 | 0.9 | 20 | 0.9 | 31 | 0.8 | 23 | 1.5 |
| Hyperhidrosis | 68 | 0.9 | 14 | 0.6 | 33 | 0.8 | 20 | 1.3 |
| Vomiting | 60 | 0.8 | 13 | 0.6 | 34 | 0.8 | 13 | 0.9 |
| Insomnia | 51 | 0.6 | 14 | 0.6 | 27 | 0.7 | 10 | 0.7 |
| Diarrhea | 36 | 0.5 | 10 | 0.5 | 15 | 0.4 | 11 | 0.7 |
| Restlessness | 27 | 0.3 | 11 | 0.5 | 12 | 0.3 | 4 | 0.3 |

* multiple mentioning was possible

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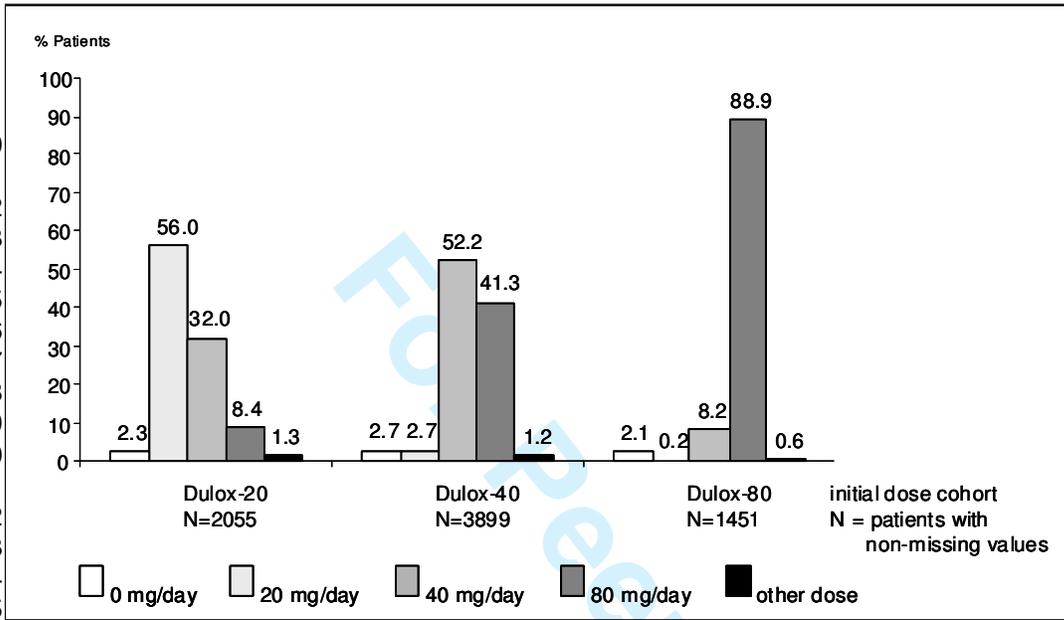


Figure 1 Doses of duloxetine at Week 12 by initial dose cohorts

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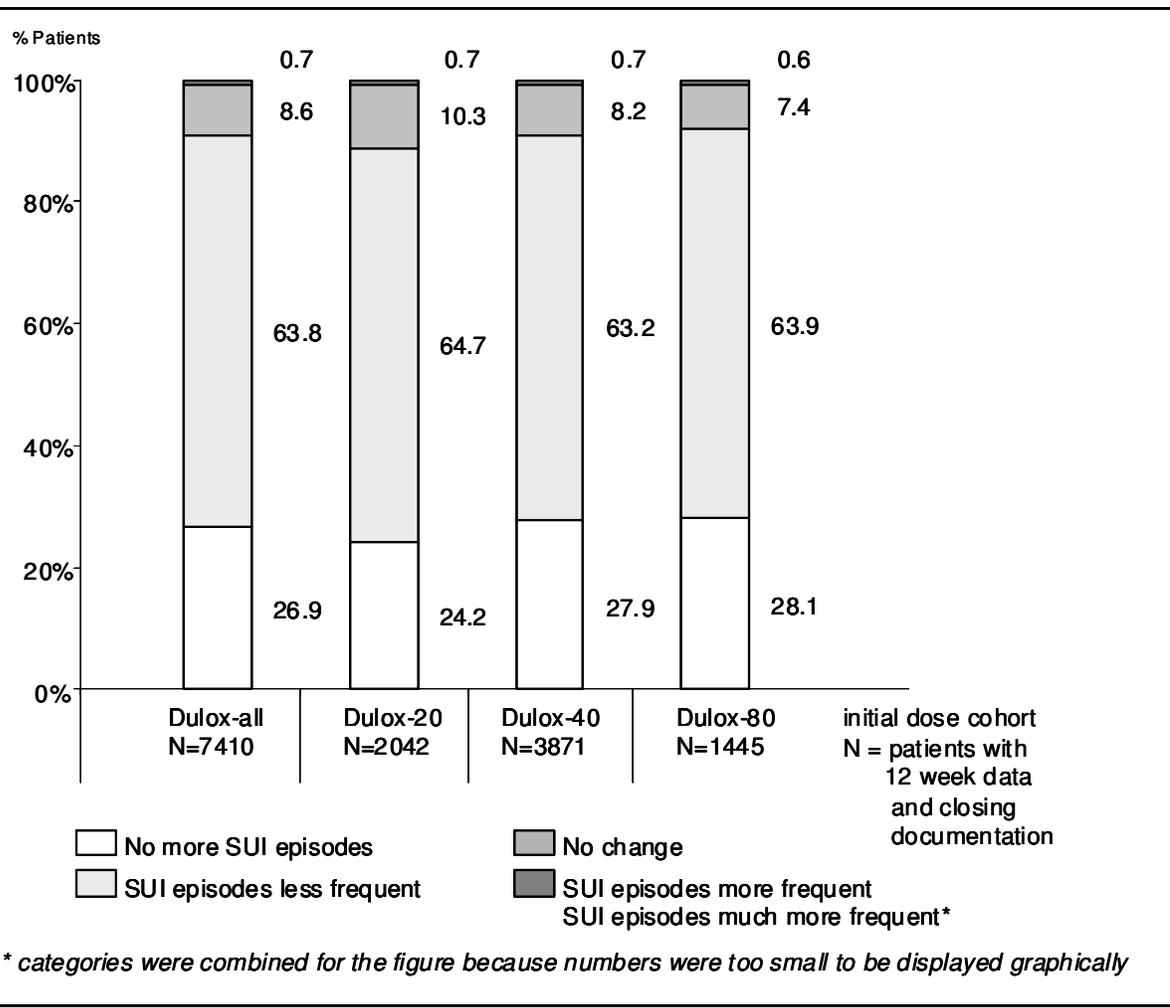


Figure 2 Perceived change in SUI episode frequency at Week 12 (compared to baseline)



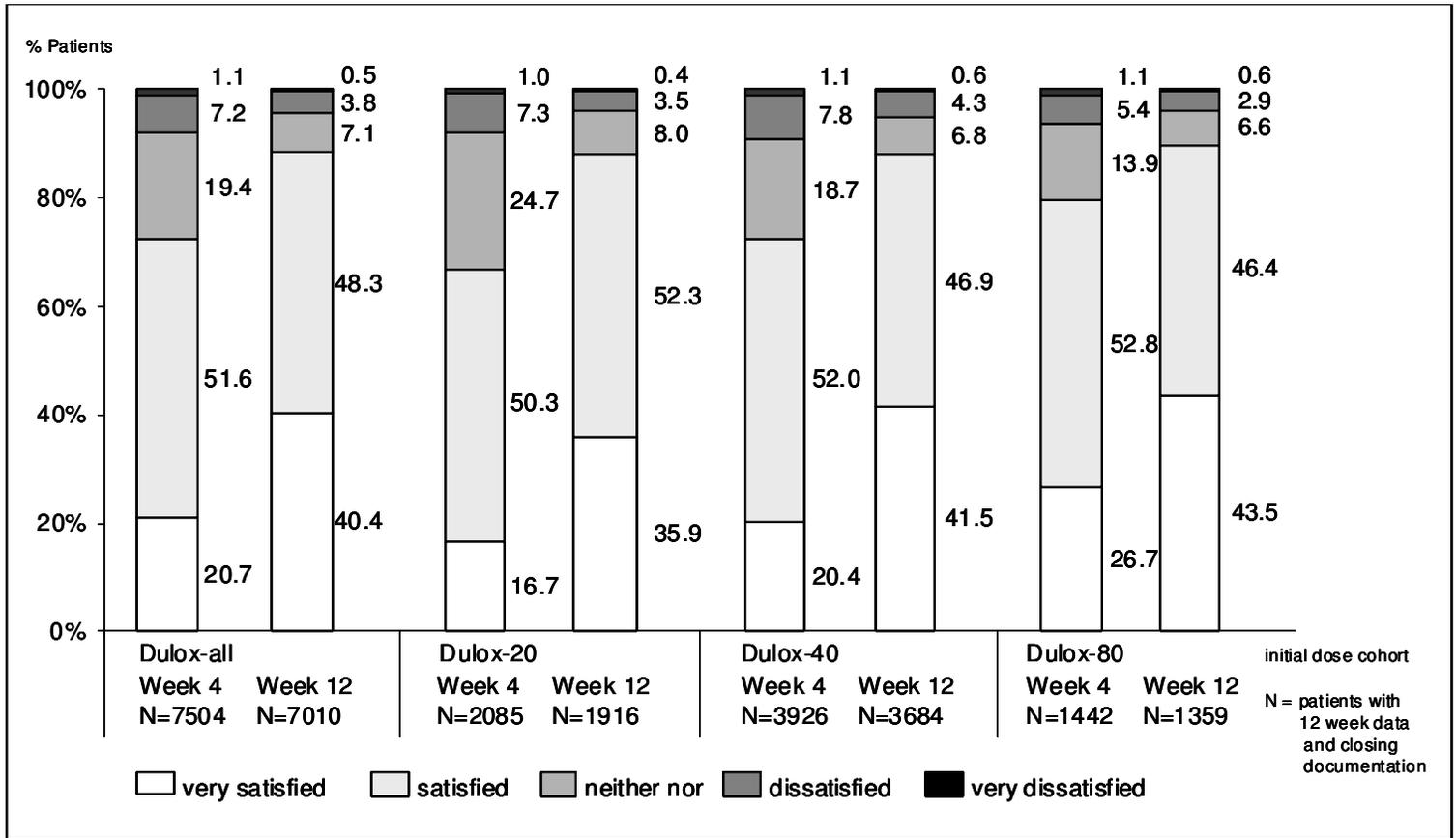


Figure 3 Patient satisfaction at Week 4 and Week 12

Only