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SAFETY AND TOLERABILITY OF DULOXETINE IN THE TREATMENT OF FEMALE STRESS URINARY INCONTINENCE (SUI) IN GENERAL PRACTICE IN GERMANY - RESULTS FROM A LARGE OBSERVATIONAL STUDY

Aims of study
Primary objective of the study was to evaluate the safety and tolerability of duloxetine in the treatment of female SUI in a large sample of patients treated in routine clinical practice. Specifically, we aimed to detect possibly unknown uncommon adverse events (AEs), and the influence of confounding factors on the safety and tolerability profile of duloxetine.

Study design, materials and methods
DUROSA ("DUloxetine ROutine SAfety") was a two-armed, multicenter, prospective, observational study, documenting women aged ≥18 years with symptoms of SUI, who were initiated to conservative treatment either with duloxetine (DULOX) or any other conservative SUI therapy (OTHER) in urologist, gynecologist and primary health care practices. It was planned to document about 1 OTHER for every 2 DULOX patients. Due to the observational design, patients were not randomized to treatment cohorts; the treatment decision was entirely at the discretion of the physician. No statistical comparisons were performed between the two groups. At baseline, the patients' age, BMI, menopausal state, parity, duration and severity of SUI, previous and current SUI therapy, relevant concomitant diseases and co-medications were documented. Further documentation, including AEs and early discontinuation, was scheduled after 4 and 12 weeks of treatment. On recommendation of the EMEA, an additional 24-week follow-up and a short baseline screen for depressive core symptoms and suicidality were introduced, but restricted to primary health care physicians, who could routinely observe their patients over this period. The presented data refer to this subgroup of patients only. Evaluation was largely descriptive; to assess the association of relevant confounding factors with occurrence of AEs in the DULOX cohort, step-wise log-linear regression models were applied.

Results
This analysis comprises 5879 patients (4010 DULOX, 1869 OTHER). Patient characteristics and baseline data were largely similar in DULOX and OTHER patients, except for urge urinary incontinence related medication (1.8% vs. 14.7%; Table 1).

Table 1. Patient Characteristics and Baseline Values

	DULOX (N=4010)	**OTHER (N=1869)**
Age, mean (±SD)	63.1 (±12.7)	61.5 (±12.9)
BMI, mean (±SD)	27.6 (±4.3)	27.1 (±4.3)
No. of child deliveries, mean (±SD)	2.0 (±1.3)	1.9 (±1.3)
Incontinence episode frequency (per week) mean (±SD)	10.9 (±10.2)	9.9 (±9.2)
Duration of SUI (months) mean (±SD); median	43.3 (±56.9); 24	44.0 (±61.0); 23
Post-menopausal	3370 (84.0%)	1524 (81.5%)
Any comorbidity	2892 (72.1%)	1266 (67.7%)
Hypertension	2175 (54.2%)	911 (48.7%)
Lipid metabolism disorder	1419 (35.4%)	646 (34.6%)
Diabetes	905 (22.6%)	413 (22.1%)
Depression	681 (17.0%)	300 (16.1%)
Heart disease	517 (12.9%)	197 (10.5%)
Any concomitant medication	2463 (61.4%)	1142 (61.1%)
Urge urinary incontinence medication	73 (1.8%)	274 (14.7%)
Antidepressant	433 (10.8%)	209 (11.2%)
Any previous SUI treatment	1808 (45.1%)	802 (42.9%)
Previous SUI surgery	94 (2.3%)	41 (2.2%)

In both groups, >16% of patients had a baseline diagnosis of concomitant depression. Results from the screen for depressive core symptoms and suicidality indicated a most likely underlying depressive disorder in 15.6% DULOX and 13.2% OTHER patients, suicidal ideation in 9.8% and 8.5%, tendencies towards self harm in 4.4 and 5.0%, and a history of suicide attempts in 1.7% and 1.6%, respectively. In both groups about 11% received concomitant antidepressant medication, <0.3% had duloxetine as an antidepressant.

Table 2. Summary of Adverse Events

	DULOX	OTHER
Patients observed	4010 (100%)	1869 (100%)
Any AE	365 (9.1%)	107 (5.7%)
Serious adverse events (SAE)	19 (0.5%)	8 (0.4%)
AEs l/t discontinuation	79 (2.0%)	14 (0.8%)
AEs with lethal outcome	8 (0.2%)	3 (0.2%)

While AE prevalence was higher in DULOX than in OTHER patients (9.1% vs. 5.7%, Table 2), SAE-rates and rates of early termination (5.7% vs. 4.2%) were similar in both treatment groups. AEs reported in at least 0.5% of DULOX patients were: nausea 87 (2.2%), dry mouth 44 (1.1%), dizziness 33 (0.8%), fatigue 30 (0.8%), sleep disorder 26 (0.7%) and headache 20 (0.5%). In

OTHER patients any AE-type was reported in less than 0.5%. Depression as an AE was reported in 4 (<0.1%) DULOX and 2 (0.1%) OTHER patients. In 3 DULOX patients SAEs were judged therapy related: 1 confusional state with dermatozoon delusion, 1 acute abdomen with subileus and urinary retention, and 1 severe gastritis. OTHER patients did not report any related SAE. Death occurred in 0.2% of either group (DULOX: 1 road traffic accident, 1 intestinal infarction, 1 sepsis and multi-organ failure, 3 cardiac deaths, 1 diverticulitis, 1 death of unknown cause; OTHER: 1 apoplectic insult and 2 cardiac deaths); none of these was judged therapy related. The logistic regression model showed that the intake of concomitant medication, especially urge urinary incontinence medication (yes vs. no, $p<0.05$, OR >1), higher age and a higher initial DULOX dose (40 vs. 20 mg/day) were associated with higher rates of AEs, while signs of depressive disorder were associated with a lower risk (depressive disorder probable/most likely vs. unlikely/possible symptom of depressed mood, $p=0.0016$, OR 0.691). No association was found between the presence of concomitant diseases and AE-rates.

Interpretation of results

The results show that women seeking treatment for SUI in German primary health care practices form a population older and more afflicted by comorbidities than previously perceived in controlled clinical trials [1]. Median BMIs of 26 (OTHER) and 27 (DULOX) tell that more than half of the patients had overweight, a known risk factor for SUI and cardiovascular disease. Further cardiovascular risk factors as hypertension, lipid metabolism disorder, diabetes and manifest heart disease were observed in substantial percentages of patients. Taking this into account, the AE rates appear remarkably low as compared to data from controlled clinical trials [1]. However, similar discrepancies between AE rates in controlled trials and routine practice have been reported for other incontinence-related drugs [2]. Rates of SAEs and AEs with lethal outcome were similar in both treatment groups. Overall, the AEs observed in the DULOX group confirm the substance's known safety profile, no previously unrecognized safety concerns have emerged. The rates of concomitant depression and depressive symptoms observed in this study are in line with findings from epidemiological studies on late-life depression [3]. No suicidal events were reported; under duloxetine treatment baseline depressive core symptoms were even associated with a lower likelihood for the reporting of any AE.

Concluding message

Event though the observed population of SUI patients treated in general practice was found to have a higher mean age and higher prevalence of cardiovascular risk factors than patients included in previous controlled clinical trials [1], no previously unknown uncommon AEs were detected.

References

1. Eur J Obstet Gynecol Reprod Biol 2007; 125(1):120-8
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