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Female Urology - Incontinence

# Facilitatory Neuromodulative Effect of Duloxetine on Pudendal Motor Neurons Controlling the Urethral Pressure: A Functional Urodynamic Study in Healthy Women

*Sönke Boy* [a,*], *André Reitz* [a], *Barbara Wirth* [a], *Peter A. Knapp* [a], *Peter M. Braun* [b], *Axel Haferkamp* [c], *Brigitte Schurch* [a]

[a] *Neuro-Urology, Swiss Paraplegic Center, Balgrist University Hospital, Zurich, Switzerland*
[b] *Department of Urology, University of Kiel, Germany*
[c] *Department of Urology, University of Heidelberg, Germany*

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**Abstract**

***Objective:*** The aim of this functional urodynamic experiment in healthy women was to study the effect of duloxetine, which is a combined serotonin and norepinephrine (5-HT/NE) reuptake inhibitor, on urethral resting pressure, excitability of pudendal motor neurons, and urethral sphincter contractility.
***Methods:*** In 11 healthy female subjects three baseline urethral pressure profiles (UPPs) were obtained to study resting pressure. Afterward the individual motor threshold (MT) for external urethral sphincter (EUS) contraction in response to transcranial magnetic stimulation (TMS) was determined to study the excitability of pudendal motor neurons. Another three UPPs were recorded while sacral root magnetic stimulation (SMS) was performed to evoke reproducible urethral contractions to study urethral sphincter contractility. Then the women received 40 mg duloxetine and the protocol was repeated 4 h after drug administration. The resting pressure values, MT values following TMS, and the EUS pressure amplitudes in response to SMS obtained at baseline were statistically compared to the corresponding values at follow-up after duloxetine.
***Results:*** Oral administration of duloxetine significantly lowered MT for EUS contraction in response to TMS ($p = 0.013$). In addition, duloxetine significantly increased EUS pressure amplitudes in response to SMS ($p = 0.0007$, 5 of 11 subjects evaluated) but did not change urethral resting pressures.
***Conclusions:*** This is the first functional, urodynamic controlled study to show that the combined 5-HT/NE reuptake inhibitor duloxetine has a significant effect on the excitability of pudendal motor neurons and on urethral sphincter contractility in healthy women in vivo but no significant effect on urethral resting tone. Our data confirm a facilitatory neuromodulative effect of duloxetine on sphincter motor neurons in humans.


* Corresponding author. Neuro-Urology, Swiss Paraplegic Center, Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland. Tel. +41 1 386 3721; Fax: +41 1 386 3731.
E-mail address: sboy@paralab.balgrist.ch (S. Boy).

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## 1. Introduction

Stress urinary incontinence in women is a highly prevalent condition known to have an impact on quality of life in affected women [1,2]. Until recently the therapy consisted mainly of pelvic floor training or surgery in severe cases. Currently, the possibility of a medical treatment has evolved. Duloxetine as a combined serotonin and norepinephrine (5-HT/NE) reuptake inhibitor was proven to be an effective and safe drug in the treatment of stress urinary incontinence that increased quality of life [3,4]. It is thought to have a facilitatory effect on pudendal motor neurons in the Onuf nucleus and thus increase urethral sphincter activity. However, this mechanism of action known from experiments in cats has never been shown in humans [5].

The aim of this functional urodynamic experiment was to study the effect of the 5-HT/NE uptake inhibitor duloxetine on the urethral pressure in healthy women and to assess first the urethral resting pressure, second the excitability of pudendal motor neurons in response to transcranial magnetic stimulation (TMS) of the motor cortex, and third the urethral contractility in response to sacral root magnetic stimulation (SMS). To our knowledge this is the first urodynamic controlled study aiming to show that the selective 5-HT/NE uptake inhibitor duloxetine may have a significant effect on urethral resting pressures, the excitability of pudendal motor neurons and on sphincter contractility in healthy women in vivo.

## 2. Patients and methods

After approval from the local ethics committee 11 healthy women (all students from the University of Zürich) gave their written informed consent and were included in the study. Subjects with a history of recurrent urinary tract infections, stress or urge urinary incontinence, or any medication known to influence the lower urinary tract were excluded in advance. Immediately before and 2 d after the experiment, urine screening tests were done to exclude urinary tract infection. Prior to the study a pregnancy test was obtained.

### 2.1. Urodynamic measurement

Prior to the experiment the subjects were asked to empty the bladder. While the subjects were lying supine on a fluoroscopy table a microtip pressure transducer catheter (radiopaque, 8F, UNISENSOR AG, 8544 Attikon, CH) was inserted into the bladder. Using a commercially available system the catheter was pulled through the urethra with a standardized velocity of 1 mm/s and a 3 o'clock transducer orientation. When the pressure transducer left the external urethral ostium, pulling was stopped and the catheter was placed into the bladder again for the next measurement. In this fashion urethral pressure profiles (UPPs) were obtained. For determination of motor thresholds (MTs) the pressure transducer was positioned into the external urethral sphincter (EUS). Obtained pressure values ensured correct position.

### 2.2. Magnetic stimulation

Magnetic stimulation was performed with the magnetic impulses generated by a Dantec® MagPro X100 magnetic stimulator and applied by a Dantec® MCF-125 liquid-cooled magnetic coil. The maximum magnetic field strength was 1.8 Tesla. For stimulation the coil was positioned at the midline over the cranial motor cortex, and afterward under the subject at midline next to the sacrum.

First, the individual MT of the subjects was determined for TMS. Single magnetic pulses with low intensities were applied to allow the subjects to get used to the magnetic stimulation. The strength of the applied magnetic field started at 20% of the maximum stimulator output. The stimulation strength was increased slowly until a clear motor response of the external urethral sphincter (sharp pressure rises) occurred. Afterward, stimulation strength for SMS was adapted to the individual pain threshold. The individual maximal tolerable stimulation strength determined for every subject was then used during the baseline and follow-up measurements to evoke reproducible contractions of the external urethral sphincter. Frequency of the stimulation was 1 Hz.

### 2.3. Experimental procedure

The baseline protocol under continuous cardiovascular monitoring included six UPPs and determination of motor threshold for each subject. Three UPPs were performed without any intervention at rest. Afterward, motor threshold for urethral sphincter contraction in response to TMS was determined. During the subsequent three UPPs single-pulse magnetic stimulation was applied to the sacral roots with field strength above individual sacral MT. Then the women received 40 mg duloxetine. According to pharmacodynamic considerations, the follow-up measurements were done identically to the baseline protocol 4 h after drug administration because in young healthy subjects this formulation is known to reach maximum plasma level 4 h after oral intake.

### 2.4. Data analysis

The UPPs were recorded with a 1000-Hz sampling rate and further analyzed using the Soleasy™ software package (ALEA Solutions, Switzerland). Five steps of further analysis were done.

To exclude a systemic effect of duloxetine on the blood pressure and therefore on the urethral pressure, blood pressure values measured at baseline were compared to those measured during the follow-up measurement by paired t test (level of significance, $p < 0.05$).

To evaluate duloxetine-induced urethral pressure changes of the entire urethra, mean and maximal pressure values calculated over the entire urethral length at baseline were

compared to those values after duloxetine administration by analysis of variance for repeated measures with Bonferroni correction (level of significance, $p < 0.05$).

To evaluate urethral pressure changes in specific urethral segments induced by duloxetine the functional urethral length was divided into three sections, the proximal, the middle, and the distal third. Within the single sections the mean urethral pressure values at baseline were compared to those values after duloxetine administration by analysis of variance for repeated measures with Bonferroni correction (level of significance, $p < 0.05$).

To evaluate the effect of duloxetine on the excitability of pudendal motor neurons the individual MTs at baseline for TMS were compared to those measured after administration of duloxetine by Wilcoxon signed rank test.

To evaluate the effect of duloxetine on the urethral contractility the amplitudes of the urethral pressure spikes in the middle urethral third induced by magnetic stimulation of the sacral roots were measured. Then baseline values were compared separately to those measured with duloxetine by analysis of variance for repeated measures with Bonferroni correction (level of significance, $p < 0.05$).

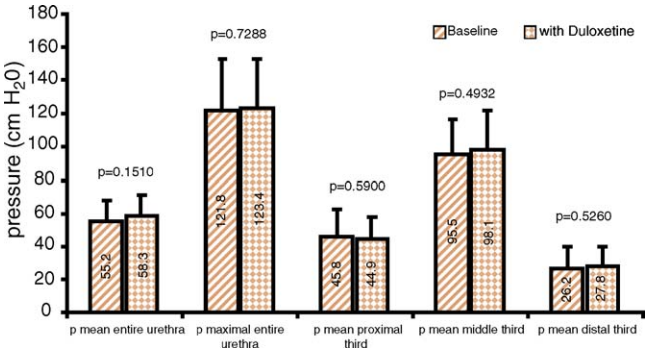


**Fig. 1 – Urethral resting pressures (mean and SD bars) before and 4 h after administration of duloxetine. Mean pressure over the entire urethra (*p* mean entire urethra), maximal pressure over the entire urethra (*p* maximal entire urethra), mean pressure over the proximal (*p* mean proximal third), middle (*p* mean middle third), and distal (*p* mean distal third) third of the urethra are shown (urethral pressure profiles *n* = 66).**

## 3. Results

The experimental procedure was well tolerated by all studied subjects. In each subject the baseline and the follow-up measurements took about 30 min to perform. Urine screening tests were all normal before as well as 2 d after the experiment. None of the subjects felt any pain or discomfort during single-pulse magnetic stimulation. Six of the 11 subjects reported tiredness, another 6 had nausea, and 3 showed a mydriasis on inspection at the follow-up 4 h after duloxetine intake. Two days later none of the subjects complained of these symptoms.

### 3.1. *Blood pressure monitoring*

In the studied population of healthy female volunteers duloxetine had no effect on the systemic blood pressure. The mean (± SD) systolic blood pressure was 118.0 ± 12.3 mm Hg at baseline and 121.0 ± 13.0 mm Hg at follow-up ($p = 0.621$). Diastolic blood pressure was 66.70 ± 7.7 mm Hg at baseline and 68.1 ± 9.4 mm Hg at follow-up ($p = 0.327$).

### 3.2. *Effect of duloxetine on the urethral resting tone*

The mean urethral pressure at rest calculated over the entire urethra length was not significantly different at the follow-up compared to the baseline measurements ($p = 0.1510$). The maximal urethral pressures at rest measured with duloxetine did not differ from those at baseline ($p = 0.7288$). For details see Fig. 1.

### 3.3. *Effect of duloxetine on different urethral segments*

When the mean urethral pressures at rest were analyzed for the proximal, middle, and distal thirds of the functional urethral length separately, no significant difference were found between the mean pressures measured at baseline and follow-up with duloxetine (Fig. 1).

### 3.4. *Effect of duloxetine on the excitability of pudendal motor neurons*

It was possible to determine individual MTs for urethral sphincter contraction in response to TMS in all subjects. MTs were significantly lower at follow-up compared to the baseline measurements ($p = 0.013$; also compare Fig. 2).

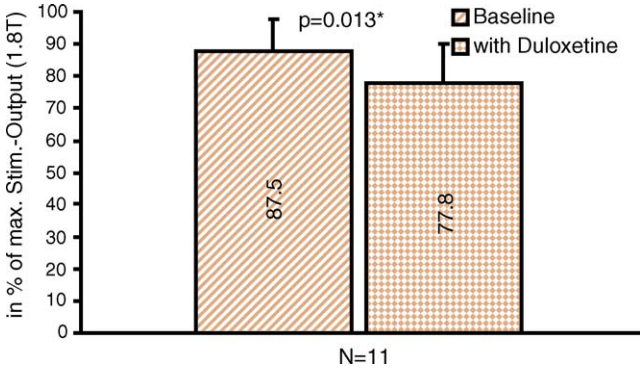


**Fig. 2 – Motor thresholds for urethral sphincter contraction in response to transcranial magnetic stimulation before and 4 h after administration of duloxetine.**

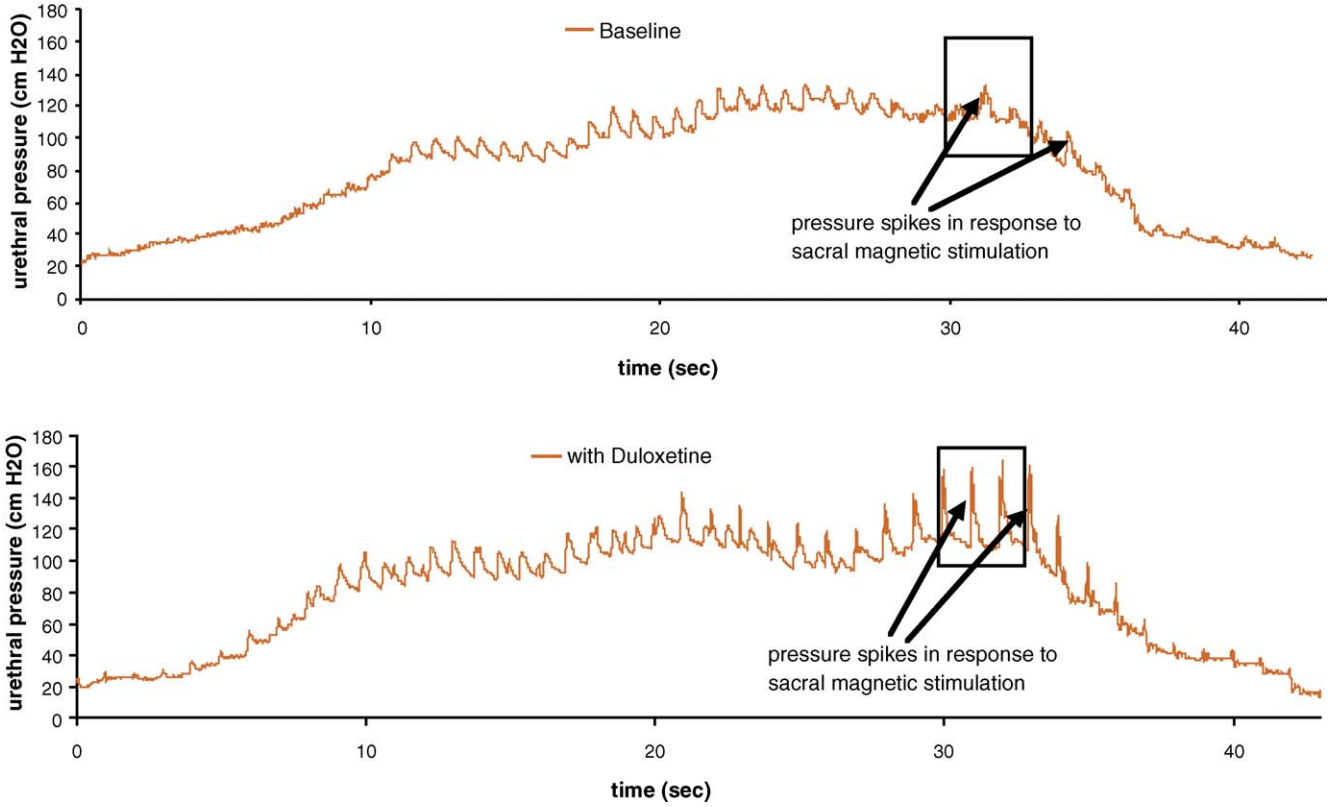


**Fig. 3 – Two urethral pressure profiles (UPPs) under single-pulse magnetic stimulation of the sacral roots for both conditions during baseline and follow-up 4 h after 40 mg duloxetine (original data from subject 11).**

### 3.5. *Effect of duloxetine on the urethral contractility (Figs. 3 and 4)*

In six women there were significant blood pressure-induced pressure rises simultaneously to pressure spikes in response to SMS, which made discrimination of signals difficult. To exclude a misinterpretation, the data of these subjects were not used to evaluate urethral contractility. In the remaining 5 subjects 5–12 spikes could be analyzed from every UPP under SMS. Amplitudes of the urethral pressure spikes in the middle urethral third evoked by magnetic stimulation of the sacral roots after administration of duloxetine were significantly higher (mean, 25.3 cm $H_2O$) compared to those at baseline (mean, 14.9 cm $H_2O$, $p = 0.0007$; also compare Fig. 5). The adjusted confidence interval for difference in means was 7.3; 13.5.

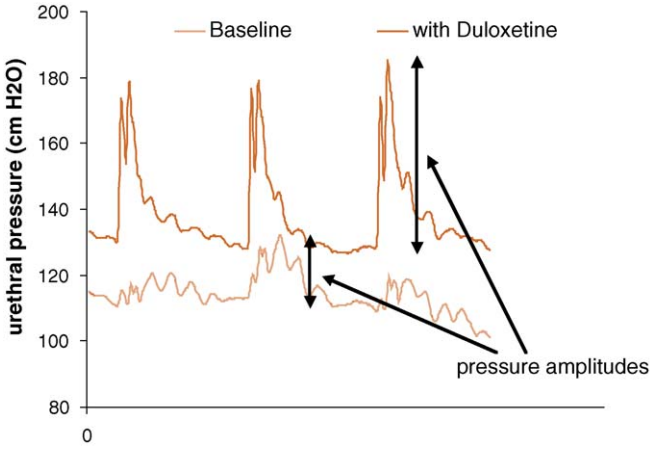


**Fig. 4 – Cut-out magnification and overlay from Fig. 3 from two UPPs during baseline and follow-up 4 h after 40 mg duloxetine (original data from subject 11).**

Oral administration of duloxetine significantly lowered the MT for urethral sphincter contraction in response to TMS ($p = 0.013$). In addition duloxetine significantly increased amplitudes of pressure spikes in response to SMS in 5 of 11 subjects (45%) whose data could be analyzed ($p = 0.0007$) but did not change urethral resting pressures.

## 4. Discussion

Until recently the therapy for stress urinary incontinence consisted mainly of pelvic floor training, off-label use of a variety of agents, and surgical procedures in severe cases [6]. Only recently has the possibility of a medical treatment evolved.

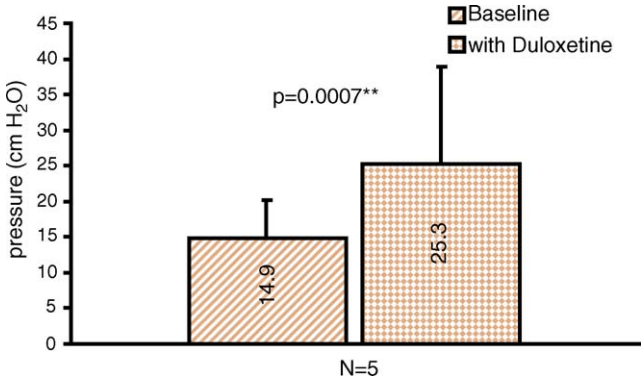


**Fig. 5 – Amplitudes of urethral pressure spikes before and 4 h after administration of duloxetine.**

Duloxetine was proven to be an effective and safe drug in the treatment of stress urinary incontinence [3,7–9]. It is a combined 5-HT/NE reuptake inhibitor. A high density of $\alpha_1$-adrenergic and 5-$HT_2$ serotonergic receptors can be found in many areas in the spinal cord associated with lower urinary tract function but there is a particularly dense representation in the Onuf nucleus [5,10–13], an area in the sacral ventral horn representing the motor neurons of the external urethral sphincter [13,14]. Serotonergic agonists generally suppress parasympathetic activity and enhance sympathetic and somatic activity in the lower urinary tract. Activation of the central serotonergic system can suppress voiding by enhancing the efferent control of the urethral outlet [15]. Noradrenergic agonists and antagonists produce effects on sympathetic and somatic activity in the lower urinary tract, which is dependent on the adrenergic receptor subtype with which the agonists and antagonists interact [7]. Urethral sphincter activity is partly centrally controlled by $\alpha_1$-adrenergic receptors. Prazosin, an $\alpha_1$-receptor antagonist was shown to influence urethral responses through a central nervous system action and not through a peripheral mechanism [16].

As a 5-HT/NE reuptake inhibitor duloxetine can be expected to have similar effects on the lower urinary tract as serotonergic and noradrenergic agonists. Studies in cats have indicated that duloxetine significantly increases bladder capacity and sphincteric muscle activity in the cat acetic acid model of irritated bladder function [13]. The results also showed that the effects of duloxetine on the bladder and sphincter were mediated centrally through both motor efferent and sensory afferent modulation [17]. These central effects of duloxetine on the bladder were reversed by the nonselective serotonergic antagonist methiothepin; the central effects on the sphincter were blocked by prazosin and LY53857, $\alpha_1$-adrenergic and 5-$HT_2$ serotonergic receptor antagonists, respectively [17]. Therefore, it is logical to assume that the effects on bladder detrusor and urethral skeletal muscle activity were mediated through temporal prolongation of serotonin and norepinephrine in the synaptic cleft [7]. The effects on the lower urinary tract were demonstrated to be unique to dual serotonin and norepinephrine reuptake inhibition in a single molecule and cannot be provoked by administration of single reuptake inhibitors alone or in combination [18]. In the animal studies described above duloxetine increased sphincter activity measured by sphincter electromyography (EMG), thus promoting the idea of improved continence by increased sphincter activity. Similar studies in humans are lacking so far but remain a future challenge to explain the finding of improved continence with duloxetine in the clinical studies mentioned above.

The results of our study show that in healthy women duloxetine had no effect on urethral sphincter tone at rest. This suggests that duloxetine acts mainly by increasing the amount of reflex activity that is generated by the neuronal network to prevent urine leakage in a stress situations such as coughing, sneezing, and physical effort. Another reason might be that an increased sphincter activity during bladder filling recorded by sphincter EMG is not necessarily reflected by an actual increase in urethral pressure [19].

In this study TMS of the motor cortex was used to study the effect of duloxetine on the excitability of pudendal motor neurons and SMS to study contractility of the urethral sphincter. Through a coil the magnetic stimulator generates a magnetic field that induces electric currents in any electrical conductive material. When applied to human tissues these magnetic fields stimulate nerves noninvasively by inducing currents and depolarization. This technique has been used for evaluating efferent nerves innervating the pelvic floor [20–22] and could establish motor latencies for the pudendal motor neurons to the external urethral and anal sphincter [23,24]. It has also been used in several urodynamic studies in healthy humans for reproducible evaluation of drug effects on sphincter behavior [25,26].

Thresholds for urethral sphincter contraction in response to TMS were significantly lowered after duloxetine intake. This suggests a facilitatory effect of duloxetine on pudendal sphincter motor neurons causing an increased transmission rate of neuronal signals from the upper motor neuron to the lower motor neuron. Monoamines were repeatedly found to have no effect on motor threshold evaluated by TMS [27,28] ruling out the possibility that the effects

seen on MTs were transmitted via a direct effect of duloxetine on excitability of human motor cortex. This implicates the effect seen must have been evoked subcortically.

In our study urethral sphincter contractility in response to SMS was significantly increased, suggesting an increased neuronal output of pudendal sphincter motor neurons under the influence of duloxetine in response to a defined stimulus, in this case a magnetic stimulation. Magnetic stimulation of the sacral roots in combination with urethral pressure recordings is a reproducible method to evaluate sphincter contractility [20,25,26,29,30]. It is not entirely clear what is stimulated by the magnetic coil. Both direct stimulation of efferent fibers to the EUS as well as a reflex EUS response via the afferent pathways are a possibility. In a previous study with the same experimental setup [20,30], it was concluded based on the measured latencies that SMS stimulates mainly afferent fibers and the responses are reflexly mediated. That is why the finding of increased contractility of the urethral sphincter is probably centrally mediated by duloxetine on sphincter motor neurons. Although a significant effect on contractility could be shown the results for this parameter should be interpreted carefully because of the low number of subjects evaluated.

Further studies are required to evaluate the exact site of drug action and to evaluate the effect of duloxetine on sacral reflex pathways.

## 5. Conclusion

To our knowledge this is the first functional, urodynamic controlled study to show that the combined 5-HT/NE reuptake inhibitor duloxetine has a significant effect on the excitability of pudendal motor neurons and on sphincter contractility in healthy women in vivo. Our data show that the thresholds for urethral pressure responses after TMS are lowered and amplitudes of pressure spikes in response to magnetic stimulation of the sacral roots are increased, whereas there is no significant effect of duloxetine on urethral resting tone. These results indicate that the effect of duloxetine on the EUS is mainly centrally mediated by acting facilitatory on pudendal motor neurons controlling the urethral tone.

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