

# Effect of single doses of citalopram and reboxetine on urethral pressure: A randomized, double-blind, placebo- and active-controlled three-period crossover study in healthy women

Thea Christoffersen<sup>1,2</sup>  | Jonatan Kornholt<sup>1</sup>  | Troels Riis<sup>1</sup> | Jesper Sonne<sup>1</sup> | David P. Sonne<sup>1,2</sup>  | Niels Klarskov<sup>2,3</sup> 

<sup>1</sup>Department of Clinical Pharmacology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark

<sup>2</sup>Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

<sup>3</sup>Department of Gynecology and Obstetrics, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark

## Correspondence

Thea Christoffersen, MD, Department of Clinical Pharmacology, Bispebjerg Bakke 23, 2nd floor, 2400 Copenhagen, Denmark.  
Email: [thea.christoffersen@regionh.dk](mailto:thea.christoffersen@regionh.dk)

## Funding information

Department of Clinical Pharmacology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen

## Abstract

**Aims:** Urethral closure function is essential for urinary continence in women and decreased urethral pressure is associated with stress urinary incontinence (SUI). For decades, the effects of serotonergic drugs on central neural control of urethral closure have been investigated and discussed. Epidemiological studies suggest that the use of selective serotonin reuptake inhibitors (SSRIs), such as citalopram, is associated with SUI. However, the literature findings are conflicting. This study aimed to evaluate citalopram's effect on opening urethral pressure (OUP) in healthy women.

**Methods:** We conducted a randomized, double-blind, placebo- and active-controlled crossover study in 24 healthy women. On three study days, which were separated by 8 days of washout, the subjects received single doses of either 40 mg citalopram (and placebo<sub>reboxetine</sub>), 8 mg reboxetine (and placebo<sub>citalopram</sub>), or two placebos. Study drugs were administered at a 1-h interval due to a difference in estimated time to peak plasma concentration ( $t_{max}$ ). We measured OUP with urethral pressure reflectometry under both resting and squeezing conditions of the pelvic floor at estimated  $t_{max}$  for both study drugs (one timepoint).

**Results:** Compared to placebo, citalopram increased OUP by 6.6 cmH<sub>2</sub>O (95% confidence interval [CI] 0.04–13.1,  $p = 0.048$ ) in resting condition. In squeezing condition, OUP increased by 7.1 cmH<sub>2</sub>O (95% CI: 1.3–12.9,  $p = 0.01$ ). Reboxetine increased OUP by 30.0 cmH<sub>2</sub>O in resting condition compared to placebo (95% CI: 23.5–36.5,  $p < 0.001$ ), and 27.0 cmH<sub>2</sub>O (95% CI: 21.2–32.8,  $p < 0.001$ ) in squeezing condition.

**Conclusion:** Citalopram increased OUP slightly compared to placebo suggesting that SSRI treatment does not induce or aggravate SUI.

**KEYWORDS**

citalopram, noradrenaline reuptake inhibitor, reboxetine, selective serotonin reuptake inhibitor, stress urinary incontinence, urethral pressure reflectometry

## 1 | INTRODUCTION

Stress urinary incontinence (SUI) is the involuntary leakage of urine during moments of physical activity that increases the intraabdominal pressure, including coughing, sneezing and physical exertion.<sup>1</sup> In women, urinary continence depends on the coordinated activity of the urinary bladder, the bladder neck, the urethra, the urethral sphincter, as well as supporting structures. Urethral pressure is crucial for urethral closure function and must be higher than the bladder pressure to maintain continence both during rest and during sudden increases in abdominal pressure (i.e., stress episodes).<sup>2</sup> Accordingly, urethral pressure is observed to be decreased in women with SUI compared to healthy controls.<sup>3</sup>

The complex neural control of the urethral pressure during storage and occasional elimination of urine involves parasympathetic, sympathetic, and somatic pathways. Somatic modulation of urethral pressure is exerted through the pudendal nerve, which innervates the external urethral sphincter. The pudendal motor nucleus of the sacral spinal cord is densely innervated by serotonergic (5-hydroxytryptamine [5-HT]) and noradrenergic nerve terminals.<sup>4</sup> Pharmacological agents activating 5-HT and noradrenergic receptors can therefore affect the urethral pressure. Examples include duloxetine, a serotonin noradrenalin reuptake inhibitor (SNRI), and reboxetine, a noradrenalin reuptake inhibitor.<sup>5</sup> These agents increase the urethral pressure via enhanced pudendal nerve stimulation to the external urethral sphincter.<sup>4</sup> Randomized trials have demonstrated that duloxetine treatment can decrease the symptom load of SUI, and based on these data, duloxetine is approved for treatment of moderate-to-severe SUI in some countries.<sup>6</sup>

Results from previous animal experiments have given rise to the view that 5-HT receptors generally inhibits micturition and enhance urinary continence.<sup>7,8</sup> More recently, this concept has been challenged with the identification of numerous inhibitory and excitatory subtypes of the 5-HT receptor family.<sup>9</sup> However, the exact effects of 5-HT receptor modulation on urethral continence, including subtype-specific effects, are not fully characterized. Animal data suggest that activation of the serotonin subtype 5-HT<sub>2C</sub> and 5-HT<sub>7</sub> receptors increases urinary continence reflexes and inhibits micturition in

rats.<sup>10–12</sup> These results formed the basis for a randomized, placebo-controlled study evaluating the effect of a selective 5-HT<sub>2C</sub> receptor agonist (ASP2205) on urethral pressure in healthy women. Contrary to expectations, the 5-HT<sub>2C</sub> receptor agonist exerted a dose-dependent decrease in urethral pressure compared to placebo.<sup>13</sup> Yet, a recent study demonstrated that another selective 5-HT<sub>2C</sub> agonist (TAK-233) lowered the threshold for urethral sphincter contraction induced by transcranial magnetic stimulation in healthy women, indicating that 5-HT<sub>2C</sub> receptors might enhance the active urethral-closing reflex rather than the resting urethral pressure.<sup>14</sup>

Meanwhile, several epidemiological studies have demonstrated a positive association between exposure to serotonergic antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), and urinary incontinence.<sup>15,16</sup> Taken together, these findings question the notion that stimulation of centrally-activated 5-HT receptors generally enhances continence. On the contrary, treatment with SSRIs seems to decrease urethral pressure potentially inducing or aggravating SUI.

Considering the substantial use of SSRI in women,<sup>17</sup> as well as recent studies indicating impairment of urethral closure upon 5-HT receptor activation, we did a randomized, placebo-controlled study examining the effect of citalopram, an SSRI, and reboxetine on opening urethral pressure (OUP) in healthy female volunteers.

## 2 | MATERIALS AND METHODS

Regulatory approvals were obtained from the Regional Ethics Committee (approval number: H-19011020) and the Danish Medicines Agency (EudraCT 2019-000059-14). The study was conducted according to Good Clinical Practice (GCP) and the local GCP unit monitored the study. The study was registered on ClinicalTrials.gov (NCT04097288) and written informed content was obtained from all subjects before study related procedures. Funding was provided by the clinical department.

### 2.1 | Study design and subjects

This was a randomized, double-blind, placebo- and active-controlled three-way crossover study designed to assess the effect of citalopram and reboxetine on urethral

pressure in healthy women. Subjects were recruited for this study by advertisement. The inclusion criteria were age 18–55 years, body mass index 18.5–30.0 kg/m<sup>2</sup>, and regular use of safe contraceptive methods. Major exclusion criteria were any history or evidence of clinically significant disease, including any history or symptom of urinary incontinence, urinary retention, or overactive bladder, known QT prolongation or congenital long QT syndrome, smoking and drug abuse within 3 months before inclusion, pregnancy, breastfeeding, or use of any drugs (except for paracetamol (up to 4 g/day) and hormonal contraception).

## 2.2 | Randomization and blinding

The Capital Region Pharmacy manufactured the blinded dosing kits and performed the randomization. The subjects were assigned consecutive randomization numbers (1–24), which corresponded to one of six possible treatment sequences. A Latin Square design balanced for the period was used (see Supporting Information Data). Study investigators, outcome assessor (performing urethral pressure reflectometry [UPR] measurements), other trial personnel, and subjects were blinded to sequence allocation throughout the study period.

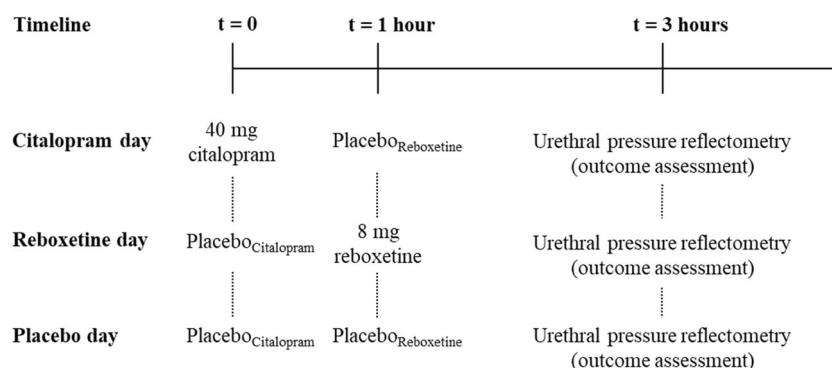
## 2.3 | Interventions and assessments

Each subject attended three study days at the research clinic. On each study day, pregnancy was excluded with a urine pregnancy test. Subjects subsequently received single oral doses of either 40 mg citalopram (and placebo<sub>reboxetine</sub>), 8 mg reboxetine (and placebo<sub>citalopram</sub>),

or two placebos. Due to different estimated time to peak plasma concentrations ( $t_{\max}$ ) for citalopram (3 h<sup>18</sup>) and reboxetine (2 h<sup>19</sup>), the study medicine was administered at two time points with a 1-h interval (Figure 1).

Citalopram was selected because it is one of the most commonly used SSRIs in Denmark and has a short  $t_{\max}$ .<sup>20</sup> Reboxetine and esreboxetine, the S,S-enantiomer of reboxetine, have previously been shown to increase the urethral pressure in doses of 4 mg (esreboxetine) and 12 mg (reboxetine).<sup>3,5</sup> We chose a dose of 8 mg reboxetine as active control to reflect a more clinically relevant and tolerable dose compared to previous studies.<sup>19,21</sup> Study days were separated by a minimum of 8 days of washout, corresponding to approximately 5.5 half-lives of citalopram (and 15 half-lives of reboxetine), and based on these elimination data, we estimated complete washout of the study drugs between study days (i.e., no carry-over effect).<sup>19,22</sup>

UPR is a sensitive and highly reproducible method for measuring urethral pressure changes induced by pharmacological treatment.<sup>5</sup> UPR measurements were performed 2 and 3 h after ingestion of reboxetine/placebo and citalopram/placebo, respectively (Figure 1). Subjects were assessed as described elsewhere.<sup>5,23</sup> Initially, the bladder was emptied by one-time catheterization. Subsequently, 150 ml 37°C 0.9% saline water was instilled in the bladder and 10 consecutive UPR measurements were performed during relaxation and five UPR measurements during squeeze (voluntary contraction of the pelvic floor). After the UPR measurements, anal pressure was assessed using anal acoustic reflectometry during relaxation and squeeze (results will be published separately). All measurements were performed with the same equipment and by the same study nurse. Adverse events (AEs) were collected at the end of each study day, by telephone the day after each study day, and 8 days after



**FIGURE 1** Timeline for study days. The figure shows the timeline for the study days in the three-way crossover study. The administration of citalopram and reboxetine were staggered due to a 1-h difference in  $t_{\max}$ . To ensure complete blinding, we had two placebos (placebo<sub>citalopram</sub> and placebo<sub>reboxetine</sub>) which were visually identical with citalopram and reboxetine, respectively. There was a washout period of at least 8 days between study days.

the last study day. All AEs were graded and relation to the study drugs was assessed by the blinded investigator.

## 2.4 | Outcomes

The primary outcome was mean postdose OUP under the resting condition of the pelvic floor on citalopram days compared to placebo days. Secondary outcomes were mean postdose OUP under resting condition on reboxetine days compared to placebo and mean postdose OUP under squeezing condition on citalopram and reboxetine days compared to placebo. From previous studies with a similar methodology,<sup>5,23</sup> we have found that predose (baseline) OUP measurements do not increase the precision of the treatment estimate as the day-to-day variability is the same as the within-day variability (data not published). Based on these analyses, and due to ethical considerations, we chose to perform UPR measurements at one timepoint postdose.

## 2.5 | Statistical analysis

The sample size for the study was estimated using power simulation with the subject, drug (citalopram, reboxetine, placebo), and period as variables. We did not model the carry-over effect due to adequate washout between study days.<sup>24</sup> From previous similar studies, we estimated a within-subject standard deviation (root mean square error) of 5.4 cmH<sub>2</sub>O.<sup>3</sup> Based on these data, we estimated a power of 99% to detect a clinically relevant difference in UOP of 10 cmH<sub>2</sub>O (between citalopram and placebo) with 24 subjects. A two-sided significance level of 5% was applied. The mean differences (citalopram vs. placebo and reboxetine vs. placebo) in OUP were analyzed using SAS' *proc glm* with the subject, treatment, and period as fixed effects.<sup>24</sup> We used SAS® Enterprise guide version 7.1 and created figures in GraphPad Prism® version 9.2.

## 3 | RESULTS

### 3.1 | Subjects

We included and randomized 24 women in the study. All subjects completed the study. One subject repeated Study Day 1 due to technical problems with the instruments. Consequently, only the second measurement was included in the analysis. Baseline characteristics of the included subjects are shown in Table 1.

TABLE 1 Demographics of the subjects

	All subjects (n = 24)
Age, years	25 (18–51)
Weight, kg	67.5 (54–87)
Body mass index, kg/m <sup>2</sup>	23.5 (18.6–28.7)
Systolic blood pressure (baseline), mmHg	113 (98–126)
Diastolic blood pressure (baseline), mmHg	71 (54–83)
Heart rate (baseline), beats/min	61 (40–77)

Note: Data are presented as median with range in parentheses.

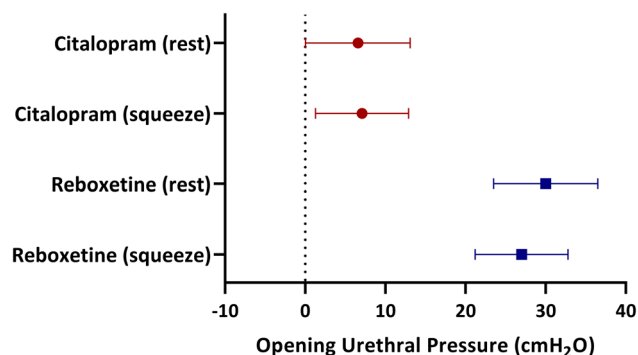


FIGURE 2 The placebo-corrected treatment effect for resting and squeezing condition. Values are differences in mean opening urethral pressure (cmH<sub>2</sub>O) with 95% confidence intervals.

### 3.2 | Urethral pressure reflectometry

Citalopram increased OUP by 6.6 cmH<sub>2</sub>O (95% confidence interval [CI]: 0.04–13.1,  $p = 0.05$ ) under resting condition of the pelvic floor compared to placebo. Under squeezing condition, OUP increased by 7.1 cmH<sub>2</sub>O (95% CI: 1.3–12.9,  $p = 0.01$ ). The active control, reboxetine, increased OUP by 30.0 cmH<sub>2</sub>O in resting condition compared to placebo (95% CI: 23.5–36.5,  $p < 0.001$ ), and under squeezing condition by 27.0 cmH<sub>2</sub>O (95% CI: 21.2–32.8,  $p < 0.001$ ) (Figure 2).

### 3.3 | Adverse events

Seventeen subjects reported 67 AEs during the study. No serious AE occurred. Most of the events (64 of 67 events) were assessed as drug-related AEs (adverse drug reaction [ADR]) by the blinded investigators. One ADR was graded as moderate (dizziness). All other ADRs were graded mild. The ADRs are listed in Table 2. There was one AE related to the UPR measurement, that is, one

TABLE 2 Adverse drug reactions

	Citalopram	Reboxetine	Placebo
Nausea	11	7	0
Dizziness	4	6	0
Drowsiness/sedation	2	3	0
Insomnia	4	7	1
Headache	5	1	1
Depressed mood	2	2	1
Paresthesia	1	3	0
Decreased appetite	1	0	0
Ear congestion	0	1	0
Dry mouth	0	1	0
Total	30	31	3

subject experienced an involuntary loss of urine the day after the procedure. Two events, diarrhea (for 5 days) and dry eyes (for 17 days), were considered unrelated to the study drug (placebo).

## 4 | DISCUSSION

In this randomized, double-blind, placebo- and active-controlled crossover trial conducted in healthy women, single-dose 40 mg citalopram increased OUP slightly, whereas single-dose 8 mg reboxetine increased OUP markedly, compared to placebo. The small increase in OUP induced by citalopram indicates that SSRI treatment is unlikely to reduce the urethral pressure, a key pathophysiological trait in women with SUI. This finding, however, contrasts with several observational studies demonstrating the increased risk of urinary incontinence among women exposed to SSRIs.<sup>15,25,26</sup> There are several potential explanations for this divergence. The increased risk of urinary incontinence in this population might be explained by uncontrolled confounders, for example, confounding by indication. Accordingly, a longitudinal cohort study has shown that women with depression at baseline are 50% more likely to report urinary incontinence compared to women with no depression. This association was consistent even after adjustment for concurrent use of psychiatric medication.<sup>27</sup> On the other hand, a positive association between initiation of SSRI treatment and urinary incontinence could also represent a normalization of physical activity upon depression remission, thus triggering SUI.<sup>2</sup> Furthermore, pooling of all types of urinary incontinence (stress-, urgency-, and mixed urinary incontinence) in

observational studies makes it difficult to isolate a risk estimate for SUI alone. Indeed, SSRI treatment may increase the risk of urgency incontinence, but not SUI, by increasing the activity of the detrusor muscle.<sup>28</sup> Finally, the effects of single-dose treatment of citalopram may differ from long-term treatment. Nevertheless, we believe that this randomized, placebo-controlled study provides the best available evidence of the effects of citalopram on urethral pressure.

The observed effect of citalopram on urethral pressure is most likely explained by the complex action of serotonin on the lower urinary tract. Thus, the citalopram-induced increase in serotonin in the synapse might increase the activity of both agonistic and antagonistic 5-HT receptors in Onuf's nucleus leading to a minor increase in urethral pressure. These observations are in line with those of Miyazato et al.<sup>11</sup> suggesting that activation of 5-HT receptors may both inhibit and enhance urethral closure in female rats. The minor effect of citalopram on OUP demonstrated in the present study is in agreement with a preclinical study in female cats showing that the SSRI S-norfluoxetine caused only a minor improvement of continence function (small increase in bladder capacity and sphincter activity) at the highest doses, whereas duloxetine, an SNRI, produced a marked response.<sup>29</sup> Indeed, duloxetine has been shown to induce a substantial increase in urethral pressure compared to placebo in human female subjects.<sup>5</sup> The marked effect of reboxetine on urethral pressure demonstrated in the present study confirms previous observations.<sup>3,5</sup> Furthermore, the effect size of 30.0 cmH<sub>2</sub>O (95% CI: 23.5–36.5) to an 8 mg dose in this study compared with 46.5 cmH<sub>2</sub>O (95% CI: 40.1–52.7) as a response to a 12 mg dose S,S-reboxetine in a previous study suggests a dose-dependent effect.<sup>5</sup> Taken together, these studies, together with our present findings, suggest that the “noradrenergic component” of antidepressants is the most likely explanation for the effect of these drugs on urethral pressure.

The study entails certain limitations. First, only healthy women were included precluding direct translation of the results to patients with established SUI. However, clinical studies have shown that the observed drug-induced increase in urethral pressure in healthy women correlates well with the clinical efficacy in patients with SUI.<sup>5,6</sup> Second, we chose to perform only one postdose UPR measurement in each treatment period. Therefore, these postdose measurements may not always coincide with the peak plasma concentration of the study drug. Theoretically, this could result in UPR measurements not reflecting the maximum pharmacodynamic potential of the drug. However, previous studies of similar single-dose design

were capable of detecting drug-induced changes in urethral pressure in healthy women, and in these studies, the time to maximal effect on urethral pressure was very close to the estimated  $t_{\max}$  of the study drugs.<sup>5,23</sup>

## 5 | CONCLUSION

Citalopram increased OUP slightly compared to placebo. This finding suggests that SSRI treatment is unlikely to decrease urethral pressure and thereby induce or aggravate SUI in women.

### AUTHOR CONTRIBUTIONS

Thea Christoffersen, Jonatan Kornholt, Jesper Sonne, Troels Riis, and Niels Klarskov designed the study and wrote the study protocol. Troels Riis, Jonatan Kornholt, and Jesper Sonne conducted the study. Troels Riis and Niels Klarskov performed data analysis. Jonatan Kornholt and Thea Christoffersen performed the statistical analysis. Thea Christoffersen drafted the manuscript. All authors critically revised the manuscript and approved the final version.

### ACKNOWLEDGMENT

The study was funded by the Department of Clinical Pharmacology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

### ETHICS STATEMENT

The study was approved by the Regional Ethics Committee of the Capital Region of Denmark (approval number: H-19011020). Written informed content was obtained from all subjects before study-related procedures.

### ORCID

Thea Christoffersen  <https://orcid.org/0000-0001-5713-2707>

Jonatan Kornholt  <https://orcid.org/0000-0003-2662-4519>

David P. Sonne  <https://orcid.org/0000-0002-4898-2256>

Niels Klarskov  <https://orcid.org/0000-0003-1906-3135>

## REFERENCES

- Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn*. 2010;29(1):4-20. doi:10.1002/nau.20798
- Ashton-Miller JA, De Lancey Jol. Functional anatomy of the female pelvic floor. *Ann N Y Acad Sci*. 2007;1101(1):266-296. doi:10.1196/annals.1389.034
- Klarskov N, Scholfield D, Soma K, Darekar A, Mills I, Lose G. Measurement of urethral closure function in women with stress urinary incontinence. *J Urol*. 2009;181(6):2628-2633. doi:10.1016/j.juro.2009.01.114
- de Groat WC, Griffiths D, Yoshimura N. Neural control of the lower urinary tract. *Compr Physiol*. 2015;5(1):327-396. doi:10.1002/cphy.c130056
- Klarskov N, Cerneus D, Sawyer W, Newgreen D, van Till O, Lose G. The effect of single oral doses of duloxetine, reboxetine, and midodrine on the urethral pressure in healthy female subjects, using urethral pressure reflectometry. *Neurourol Urodyn*. 2018;37(1):244-249. doi:10.1002/nau.23282
- Li J, Yang L, Pu C, Tang Y, Yun H, Han P. The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. *Int Urol Nephrol*. 2013;45(3):679-686. doi:10.1007/s11255-013-0410-6
- Espey MJ, Downie JW, Fine A. Effect of 5-HT receptor and adrenoceptor antagonists on micturition in conscious cats. *Eur J Pharmacol*. 1992;221(1):167-170. doi:10.1016/0014-2999(92)90788-6
- McMahon SB, Spillane K. Brain stem influences on the parasympathetic supply to the urinary bladder of the cat. *Brain Res*. 1982;234(2):237-249. doi:10.1016/0006-8993(82)90865-4
- Ramage AG. The role of central 5-hydroxytryptamine (5-HT, serotonin) receptors in the control of micturition. *Br J Pharmacol*. 2006;147(suppl 2):S120-S131. doi:10.1038/sj.bjp.0706504
- Mbaki Y, Ramage AG. Investigation of the role of 5-HT<sub>2</sub> receptor subtypes in the control of the bladder and the urethra in the anaesthetized female rat. *Br J Pharmacol*. 2008;155(3):343-356. doi:10.1038/bjp.2008.273
- Miyazato M, Kaiho Y, Kamo I, et al. Role of spinal serotonergic pathways in sneeze-induced urethral continence reflex in rats. *Am J Physiol-Ren Physiol*. 2009;297(4):F1024-F1031. doi:10.1152/ajprenal.00297.2009
- Suzuki T, Shimizu T, Kwon J, et al. Role of the serotonergic system in urethral continence reflexes during sneezing in rats. *Am J Physiol-Ren Physiol*. 2018;315(1):F79-F85. doi:10.1152/ajprenal.00614.2017
- Klarskov N, Van Till O, Sawyer W, Cernus D, Sawyer W. Effect of a 5-HT<sub>2c</sub> receptor agonist on urethral closure mechanism in healthy women. *Neurourol Urodyn*. 2019;38(6):1700-1706. doi:10.1002/nau.24045
- Kamo I, Nagata H, O'Connell G, et al. Increasing effects of selective 5-hydroxytryptamine type 2C receptor stimulation on evoked momentary urethral closure in female rats and humans. *J Pharmacol Exp Ther*. 2021;378(2):60-68. doi:10.1124/jpet.121.000573

15. Movig KLL, Leufkens HGM, Belitser SV, Lenderink AW, Egberts ACG. Selective serotonin reuptake inhibitor-induced urinary incontinence. *Pharmacoepidemiol Drug Saf.* 2002;11(4):271-279. doi:10.1002/pds.705
16. Felde G, Engeland A, Hunskaar S. Urinary incontinence associated with anxiety and depression: the impact of psychotropic drugs in a cross-sectional study from the Norwegian HUNT study. *BMC Psychiatry.* 2020;20:521. doi:10.1186/s12888-020-02922-4
17. Abbing-Karahagopian V, Huerta C, Souverein PC, et al. Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. *Eur J Clin Pharmacol.* 2014;70(7):849-857. doi:10.1007/s00228-014-1676-z
18. Cipramil. Summary of product characteristics. January 18, 2021. Accessed October 8, 2020. <http://produktresume.dk/AppBuilder/search?q=Cipramil%2C%2Bfilmovertrukne%2Btabletter%2B10%2Bmg%2C%2B20%2Bmg%2C%2B30%2Bmg%2C%2B40%2Bmg.doc>
19. Edronax. Summary of product characteristics. December 5, 2016. Accessed October 8, 2020. <http://www.produktresume.dk/AppBuilder/search?utf8=%E2%9C%93%26id=%26type=%26q=edronax%26button=S%3C%3B8g>
20. Fornis J, Pottgård A, Reinders T, et al. Antidepressant use in Denmark, Germany, Spain, and Sweden between 2009 and 2014 incidence and comorbidities of antidepressant initiators. *J Affect Disord.* 2019;249:242-252.
21. Gougoulaki M, Lewis G, Nutt DJ, Peters TJ, Wiles NJ, Lewis G. Sex differences in depressive symptoms and tolerability after treatment with selective serotonin reuptake inhibitor antidepressants: secondary analyses of the GENPOD trial. *J Psychopharmacol.* 2021;26:919-927. doi:10.1177/0269881120986417
22. Hyttel J. Citalopram—pharmacological profile of a specific serotonin uptake inhibitor with antidepressant activity. *Prog Neuropsychopharmacol Biol Psychiatry.* 1982;6(3):277-295. doi:10.1016/S0278-5846(82)80179-6
23. Kornholt J, Sonne DP, Riis T, Sonne J, Klarskov N. Effect of imipramine on urethral opening pressure: a randomized, double-blind, placebo-controlled crossover study in healthy women. *NeuroUrol Urodyn.* 2019;38(4):1076-1080. doi:10.1002/nau.23955
24. Senn S. *Cross-Over Trials in Clinical Research*. 2nd ed. John Wiley & Sons, Ltd.; 2002.
25. Moghaddas F, Lidfeldt J, Nerbrand C, Jernström H, Samsioe G. Prevalence of urinary incontinence in relation to self-reported depression, intake of serotonergic antidepressants, and hormone therapy in middle-aged women: a report from the Women's Health in the Lund Area study. *Menopause.* 2005;12(3):318-324. doi:10.1097/01.gme.0000143736.17715.55
26. Mauseth SA, Skurtveit S, Skovlund E, Langhammer A, Spigset O. Medication use and association with urinary incontinence in women: data from the Norwegian Prescription Database and the HUNT study. *NeuroUrol Urodyn.* 2018;37(4):1448-1457. doi:10.1002/nau.23473
27. Melville JL, Fan MY, Rau H, Nygaard IE, Katon WJ. Major depression and urinary incontinence in women: temporal associations in an epidemiologic sample. *Am J Obstet Gynecol.* 2009;201(5):490. doi:10.1016/j.ajog.2009.05.047
28. Candura SM, Messori E, Franceschetti GP, et al. Neural 5-HT4 receptors in the human isolated detrusor muscle: effects of indole, benzimidazolone and substituted benzamide agonists and antagonists. *Br J Pharmacol.* 1996;118(8):1965-1970.
29. Katofiasc MA, Nissen J, Audia JE, Thor KB. Comparison of the effects of serotonin selective, norepinephrine selective, and dual serotonin and norepinephrine reuptake inhibitors on lower urinary tract function in cats. *Life Sci.* 2002;71(11):1227-1236. doi:10.1016/S0024-3205(02)01848-9

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Christoffersen T, Kornholt J, Riis T, Sonne J, Sonne DP, Klarskov N. Effect of single doses of citalopram and reboxetine on urethral pressure: a randomized, double-blind, placebo- and active-controlled three-period crossover study in healthy women. *NeuroUrol Urodyn.* 2022;41:1482-1488. doi:10.1002/nau.24985