## Effect of imipramine on urethral opening pressure - a randomized, double-blind, placebo-controlled crossover study in healthy women.

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**Objectives:** Imipramine, an old tricyclic antidepressant, affects multiple neurotransmitter systems, which may affect the function of the lower urinary tract. It acts as a serotonergic and norepinephrine reuptake inhibitor, and is an antagonist to the muscarinic acetylcholine receptors and adrenergic receptors. Imipramine has previously been shown to exert beneficial effects in patients with stress urinary incontinence, where the treatment resulted in reduced symptoms and increased maximum closure pressure. However, this finding has never been confirmed in a placebo-controlled study, and imipramine is continuously being used off-label for the treatment of stress and mixed urinary incontinence. Urethral pressure reflectometry (UPR) is a reliable and repeatable technique which can detect pharmacological induced pressure changes in the urethra. The purpose of this study was to investigate the effect of single-dose imipramine on the urethral opening pressure (UOP) in healthy women using UPR.

**Materials & Methods:** A randomized, double-blind, placebo-controlled, crossover study investigating the effect of single dose 50 mg imipramine on UOP. A power calculation showed that 16 subject were needed to show a difference of 10 cm H2O with α = .05 and power = 99%. UOP was measured pre-dose and one hour post-dose (equal to tmax for imipramine) during rest and squeeze. A washout period of minimum 1 week was chosen. The study was approved by the local ethics committee and conducted according to Good Clinical Practice (GCP) guidelines.

**Results:** We recruited and included 16 subjects. All of them completed the study. Imipramine increased UOP in the resting condition with 6.5 cm H2O [95% CI: ˗0.5, 13.5], *p*  = 0.07, and in the squeeze condition with 7.9 cm H2O [95% CI ˗0.3, 16.1], *p* = 0.06.
No serious adverse events (AE) were reported. There were seven adverse drug reactions (ADRs) related to imipramine, one ADR related to placebo and two AEs related to UPR.

**Conclusions:** Imipramine insignificantly increased the UOP 6.5 cm H2O. Midodrine, duloxetine and reboxetine increased the UOP 9.3 cm H2O, 24.2 cm H2O and 44.9 cm H2O, respectively in a similar study. Thus the effect of imipramine is not clinically relevant and we do, therefore, not recommend the off-label use of imipramine for the treatment of stress urinary incontinence or mixed urinary incontinence.