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Reboxetine in therapy-resistant enuresis: A randomized placebo-controlled study

Elisabet Lundmark [a], Arne Stenberg [a], Bruno Hägglöf [b], Tryggve Nevéus [a]

[a]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

[b]Division of Child and Adolescent Psychiatry, Department of Clinical Sciences, Umeå University, Umeå, Sweden

Correspondence to: E. Lundmark, Department of Women's and Children's Health, Uppsala University, Akademiska Barnsjukhuset, SE-751 85 Uppsala, Sweden.

elisabet.lundmark@kbh.uu.se (E. Lundmark)

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Summary

Introduction
A significant minority of children with enuresis do not respond to either desmopressin or the enuresis alarm. Anticholinergics have not proven as successful as expected. The fourth evidence-based treatment, the tricyclic antidepressant imipramine, is cardiotoxic when overdosed, which has led to diminished use.

Aim
The aim was to determine whether there is a role for the noradrenergic antidepressant reboxetine, as monotherapy or combined with desmopressin, in the treatment of enuresis in children who have not responded to standard therapy, and whether there are side effects involved. We also sought prognostic factors in anamnestic data and in the voiding chart.

Patients and methods
The study was a randomized placebo-controlled study with a double-blind cross-over design, in which all patients underwent treatment during three 4-week periods, one with reboxetine 4 mg and placebo, one with reboxetine 4 mg and desmopressin, and one with double placebo treatment. The proportion of wet nights out of 14 was compared before treatment and during the last 2 weeks of each treatment period.

Results
Eighteen patients were included. The reduction of wet nights was much better with either reboxetine in monotherapy or in combination with desmopressin than during the placebo period ($p = 0.002$) (Figure). However, only one patient achieved complete dryness, this during monotherapy. There were three intermediate responders to monotherapy and five to combination treatment. With reboxetine in monotherapy, six children experienced negative side effects compared with three with combination therapy, and two with placebo. All of these side effects were mild and reversible. Only one patient chose to cease treatment because of side effects. No prognostic factors were found in either the case history or in voiding chart data.

Discussion
The present study, the first placebo-controlled trial, confirms that reboxetine is an evidence-based alternative to cardiotoxic antidepressant treatment in therapy-resistant enuresis. The fact that few patients achieved complete dryness may be due to the low dosage used. In our clinical practice we increase the dose to 8 mg when dryness is not achieved with the lower dose. Our experience is that this leaves more children with full response, but the evidence of this has yet to be shown.

Conclusion
Reboxetine seems to be an alternative in the treatment of enuretic children who have not responded to standard treatment.

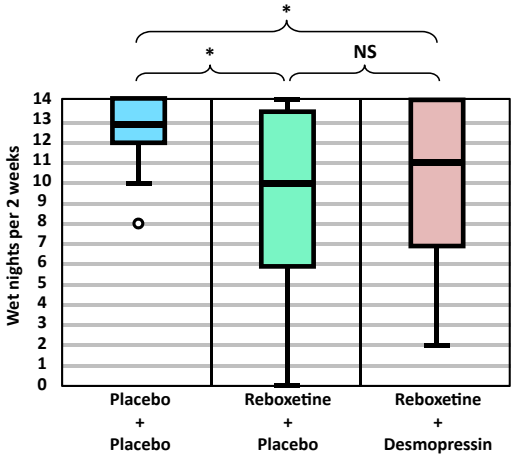

Figure The number of wet nights out of 14 with placebo, reboxetine, and combination therapy.

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Introduction

A significant minority of children with enuresis do not respond to treatment with either desmopressin or the enuresis alarm [1]. Anticholinergics have not proven as successful as expected [2], leaving a substantial amount of patients without effective treatment. The fourth evidence-based treatment of enuresis, the tricyclic antidepressant imipramine [3], probably exerts its effect via central noradrenergic stimulation, although the mechanism is not fully known. The drug's anticholinergic side effects cannot explain the anti-enuretic effect, since all imipramine-responding children in the authors' center had previously tried anticholinergic treatment without success [4]. The central noradrenergic effects of imipramine depend on the binding of the active metabolite desipramine to the locus coeruleus in the upper pons [5]. This neuron group, which is the most dense accumulation of noradrenergic neurons in the central nervous system (CNS), is crucial for both arousal from sleep and bladder function [6,7], and has direct and indirect influence on urine production via the vasopressin-producing neurons in the hypothalamus [8]. However, imipramine, as all tricyclics, is cardiotoxic when overdosed, and lethal reactions have occurred [9], which, in addition to the development of alternative antidepressants with selective serotonergic or noradrenergic action, has led to diminished use. In many countries the substance is no longer available for label prescription, which again leaves more patients without effective treatment. Considering the potentially negative psychological impact of untreated enuresis [10], it is very important to find new treatment options. The selective norepinephrine reuptake inhibitor reboxetine has the same noradrenergic action as imipramine, but no clinically relevant serotonergic effect, and no cardiotoxicity [11]. This substance has the same mode of action as atomoxetine, and has been used in pilot studies on children with neuropsychiatric disorders [12]. Selective norepinephrine reuptake inhibitors such as atomoxetine, which is used in the pediatric population, have few serious side effects. However, reboxetine is not yet registered for pediatric use.

In a pilot study the therapeutic effect was retrospectively evaluated in 61 enuretic children who, in line with clinical practice, were treated with reboxetine 4—8 mg at bedtime, combined with desmopressin if necessary. More than 50% of these children responded to treatment [13], but with the obvious drawbacks of this study design, randomized controlled trials were called for. The objective of the present study was to establish whether reboxetine has a place in the treatment of therapy-resistant enuresis, and whether there are risks and side effects involved. We also wanted to evaluate whether there was any way to predict therapy response from bladder variables and nocturnal urine production, as reflected by the case history and frequency—volume charts.

Patients and methods

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the ethics review board at the Medical Faculty of Uppsala University (dNr 2008/203). All families provided a signed informed consent.

The study was a randomized placebo-controlled study with a double-blind cross-over design. The patients meeting the criteria for inclusion were aged 7 years or more. They all suffered from severe enuresis with at least seven wet nights out of 14, and all had tried but failed treatment with desmopressin. The enuresis alarm had either been tried without effect, or deemed unfeasible because of the family situation. The enuresis did not need to be strictly mono-symptomatic according to the International Children's Continence Society (ICCS) guidelines [14], but obstipation, if present, had to be treated and daytime incontinence eradicated before the child was eligible for inclusion. The families had to be able and willing to provide a signed informed consent. Although this was not part of the inclusion criteria, all patients had either tried and failed combination therapy with anticholinergics or, because of contraindications, been unable to receive such therapy.

Patients with underlying renal, urologic, neurologic, endocrinologic, or cardiac conditions were excluded. Depression and other severe psychiatric diseases, with the exception of ADHD, were also criteria for exclusion, as was concomitant medication interfering with kidney or bladder function, sleep, or the autonomic nervous system.

Before inclusion all patients underwent a thorough physical examination, and a detailed case history, focusing on bladder and bowel habits, was taken. A uroflow examination, with measurement of residual urine, was performed, and a urinary dipstick test was done. All families were provided with a standard voiding chart to complete at home during 2 weeks. No treatment for enuresis was given during these 2 weeks. In the pre-study voiding chart daytime voiding frequency and voided volumes (day and night) were documented during 48 h, whereas wet and dry nights were recorded during 2 weeks. These recordings were used as baseline data (Table 1).

In order to exclude desmopressin responders from participation in the randomized part of the study, the 2 weeks of baseline observations were followed by 2 weeks during which the patients were given desmopressin 0.4 mg orally at bedtime. If the number of wet nights during desmopressin treatment was reduced by more than 50% compared with baseline the patient was not included in the randomized study.

After these baseline investigations the patients underwent treatment during three 4-week periods: one period with reboxetine 4 mg and desmopressin 0.4 mg treatment, one with reboxetine 4 mg and placebo, and one period with double placebo treatment. The order of these periods was blinded to patients, parents, and investigators. The randomization was made by APL Pharma Specials Inc. (Stockholm, Sweden), who also prepared the medications so that tablets were put into capsules, all of an identical design. The randomization was communicated to the investigators in sealed envelopes. Between the treatment periods a washout period of at least 48 h and at most 2 weeks was interspersed. The families recorded in a log whether the medication was taken or not and were also asked to complete new voiding diaries during all treatment periods. Side effects were actively asked for. After each