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Evaluating use of higher dose oxybutynin in combination with desmopressin for refractory nocturnal enuresis

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Summary

Introduction
Nocturnal enuresis is a common pediatric condition with limited treatment options. In older children, pharmacologic therapy is often the preferred treatment. Pharmacologic therapies including desmopressin (DDAVP) or imipramine are effective in 40–50% of children. However, imipramine has serious safety concerns. Desmopressin in combination with a fixed dose anticholinergic has been shown to be useful in individuals who fail desmopressin monotherapy, but still fails to achieve success rates greater than 60%.

Objective
The goal was to explore the efficacy and safety of using combination therapy desmopressin plus oxybutynin with increasing dose of oxybutynin in patients refractory to standard combination therapy.

Study design
This was a single institution, IRB-approved, retrospective chart review of 61 patients (ages 7–18 years) including those with monosymptomatic primary nocturnal enuresis and non-monosymptomatic enuresis with controlled daytime voiding symptoms (CDVS) treated initially with desmopressin. All patients who failed initial therapy with desmopressin were started on combination therapy desmopressin (0.6 mg) plus standard dose (5 mg) oxybutynin. In patients who failed standard combination therapy, the dose of oxybutynin was titrated upwards until a response or the maximum dose of 10 mg was achieved. Demographic and medical history data were evaluated to determine predictive factors associated with response/failure to different therapy groups.

Results
The use of escalating doses of oxybutynin in combination with desmopressin achieved an overall response rate of 96.7% defined as a 2-week period without any enuretic events following initiation of treatment. Low-dose combination therapy (LDCT) (0.6 mg of desmopressin + 5 mg of oxybutynin) had a response rate of 68% (Table). Advanced dose combination therapy (ADCT) (0.6 mg of desmopressin + 7.5–10 mg of oxybutynin) had a response rate of 75.0%. A statistically significant relationship was found correlating both attention deficit disorder/attention-deficit hyperactivity disorder(ADD/ADHD) and CDVS with failure on monotherapy. No patients in the study reported any adverse events or side effects from the medications.

Discussion
The overall success rate of 96.7% with titrated doses of oxybutynin in combination with desmopressin is considerably higher than the response rates on fixed dose combination therapy quoted in the literature and supports the need for further evaluation in larger studies. Additionally, we found a statistically significant association between monotherapy failure and children with either ADD/ADHD or controlled daytime voiding symptoms. Our study is limited by small numbers and larger studies are needed to confirm these results.

Conclusion
Our results suggest that ADCT is a safe and effective treatment option for primary nocturnal enuresis refractory to standard and low-dose combination therapy.

	Desmopressin monotherapy	LDCT	ADCT	Total
Patients treated	61	25	8	61
Responders	36	17	6	59
Response rate	59.0%	68.0%	75.0%	96.7%

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Introduction

Primary nocturnal enuresis is a common pediatric condition with an overall prevalence of 15—20% at 5 years of age with a spontaneous resolution of about 15% per year [1,2]. However, 1—2% of children at 15 years of age still suffer from nocturnal enuresis. Nocturnal enuresis may be associated with social and emotional stigmata [3]. The management of nocturnal enuresis has focused on both behavioral interventions and pharmacologic therapies. Alarm therapy achieves dryness in about two-thirds of children, presumably because of conditioning effects on arousal and/or by increasing nocturnal bladder reservoir function [4,5]. Desmopressin (DDAVP), an analogue of the antidiuretic vasopressin, increases free water absorption within the nephron decreasing the rate of fluid release into the bladder. Approximately 30% of children with nocturnal enuresis are full responders to desmopressin and 40% are partial responders with the maximal effect in children with nocturnal polyuria [6]. Imipramine is a tricyclic antidepressant, which has been demonstrated to be useful in about 50% of children [7]. Imipramine is thought to affect sleep cycle, vasopressin release, and bladder relaxation [8]. However, imipramine is currently considered a third-line therapy for nocturnal enuresis due to safety concerns and side effects, particularly the potential for cardiac toxicity and risk of fatality with overdose [8]. Neveus et al. [9] noted that anticholinergics are useful in about 40% children, often in combination with a standard dose of desmopressin. Studies to date have primarily explored the effects of combination therapy of desmopressin plus fixed dose anticholinergic therapy. We hypothesize that the use of combination therapy with titrating doses of anticholinergic therapy in individuals who failed combination therapy with fixed low-dose anticholinergic therapy will lead to an increased number of children with nocturnal enuresis being dry for 14 nights, particularly in patients with ADD/ADHD.

Material and Methods

An Institutional Review Board-approved retrospective review of all patients seen for the diagnosis of primary nocturnal enuresis (ICD-10 codes 788.36 and 788.30) during the time period November 1, 2013, to December 31, 2014, was performed. Those patients who were treated with desmopressin acetate (DDAVP) who had at least one follow-up visit were included in the study. Patients with voiding dysfunction requiring physical therapy, daytime incontinence, untreated constipation, and neurogenic bladder were excluded from the study. Patients with a history of daytime voiding symptoms that had resolved or were controlled on anticholinergic therapy were included in the study. Similarly, patients with a history constipation that was resolved or effectively being treated were included in the study. Standard bladder education was implemented in all patients, including discussing regular daytime voiding and bowel habits, prompted voiding before bedtime and avoidance of liquid intake within 2 h of bedtime. Adverse events were solicited verbally during the phone conversation or in the clinic. Families and children were asked about the more common side effects of dry mouth, facial flushing, constipation, and whether or not there were any behavioral/cognitive or other adverse effects noted since starting the medication during phone conversations or in the clinic visits.

The pharmacologic agents chosen for this study were oral desmopressin and oral oxybutynin immediate release. The initial dosing of desmopressin was 0.2 mg (0.4 mg in those who had previously tried desmopressin) with a dose increase of 0.2 mg with any failure to achieve complete response at 2-week intervals, until the maximum dose of 0.6 mg. Those children who failed maximum-dose desmopressin, were offered combination therapy with maximum-dose desmopressin plus oxybutynin 5 mg initially. The oxybutynin dose was increased in increments of 2.5 mg every 2 weeks to a maximum dose of 10 mg of oxybutynin each night in addition to the desmopressin. Telephone contact occurred during the dose titration interval until an effective dose had been achieved or maximal doses of desmopressin and oxybutynin had been tried. Maximum-dose desmopressin (0.6 mg) plus 7.5 or 10 mg of oxybutynin was defined as advanced dose combination therapy (ADCT).

Failure to respond was defined as any enuretic event occurring while on treatment during a 2-week period. Response was defined as a minimum of 14 consecutive nights of complete dryness. Enuretic episodes on nights where medication was withheld, either because of lack of fluid restriction or forgetting to take the medication, were not considered failures in this study. Table 1 lists the categories of data abstracted from the medical records of all patients included in the study. Data analysis was performed using logistic regression.

Results

Sixty-one patients (38 males and 23 females) aged between 7 and 18 years with an average age of 11.6 years (standard deviation 2.6) met the inclusion criteria. Of the 61 patients included in our analysis, total dryness (defined as zero wet nights for 2 weeks following initiation of therapy) was achieved in 36/61 (59%) of patients using desmopressin monotherapy (0.2—0.6 mg). All 25 patients who failed to be dry for 14 nights on desmopressin monotherapy chose to be treated with combination therapy. Twenty-five patients were further treated with low-dose combination therapy, maximum-dose desmopressin (0.6 mg) plus 5 mg oxybutynin immediate release. In this group of patients, complete dryness was achieved in 17 of 25 patients (68%). Eight patients in our study went on to receive ADCT, 7.5—10.0 mg of oxybutynin in combination with 0.6 mg of desmopressin. Success was noted in six out of eight (75%) of the children using ADCT (Fig. 1). No child discontinued therapy because of adverse effects. There were no reported side effects with desmopressin monotherapy. No child required treatment for dry mouth or constipation, or experienced central nervous system-related side effects with oxybutynin 5—10 mg. Serum sodium levels were not obtained in these children.

Using demographic data collected from the medical records we were able to identify factors which may predict the outcome of both monotherapy and combination therapy (Table 2).