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Imipramine for refractory daytime incontinence in the pediatric population

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Summary

Introduction and objective
Lower urinary tract (LUT) and voiding dysfunction constitute a large percentage of pediatric urology referrals. Children with urinary incontinence unresponsive to behavioral modifications and traditional pharmacotherapy including anticholinergics and alpha blockers remain a challenge. We evaluated the impact of imipramine on treatment outcomes in children with refractory incontinence.

Study design
Children ≤18 years of age with refractory non-neurogenic daytime incontinence prescribed imipramine were identified. Patient demographics and baseline testing were assessed, as well as medication dosing and side effects of all patients. The Vancouver Symptom Score (VSS) was completed at the initial consultation and each subsequent clinic visit. The questionnaire was self-administered and completed by patients and/or parents. Treatment success was defined as per the International Children's Continence Society (ICCS).

Results
One hundred and three patients (55 males and 48 females) met the inclusion criteria. The intention-to-treat response rate was 65% (complete 44, partial response 23). Sixteen (15.6%) patients were non-responders and 20 (19.4%) were lost to follow-up. There was no statistical difference between all groups with regards to age, baseline VSS, and dose. Of those children with complete follow-up ($n = 83$), 44 (53%) experienced complete treatment response. Pre- and post-VSS were statistically different in both complete and partial response groups (complete 19.5–9.5; $p < 0.0001$; partial 19.7–13; $p = 0.0002$) (Table). Side effects were reported by 11 out of 83 (13.3%) patients; partial responders experienced a higher likelihood of side effects (26.1%; $p = 0.03$).

Discussion
The mainstay of LUT dysfunction management in children is implementation of a bowel program and timed voiding regimen, with additional treatment modalities and pharmacotherapy added depending upon prevailing symptomatology. Daytime incontinence refractory urotherapy, anticholinergics, and/or non-selective alpha blockers can be difficult to treat, and can be unresponsive to parasacral transcutaneous electrical nerve stimulation (TENS) and percutaneous tibial nerve stimulation (PTNS). We observed that over half of children with refractory daytime incontinence reported complete resolution of daytime accidents with imipramine. Limitations of the study include the retrospective nature, relatively small sample size and lack of control group.

Conclusions
Two-thirds of children with refractory daytime incontinence experienced treatment response to imipramine, adding a valuable tool to the pediatric urologist's armamentarium in managing select, challenging patients.

Table Pre- and post–Vancouver Symptom Scores (VSS) were statistically different in both complete and partial response groups.

	Pre-VSS	Post-VSS	p
Complete response (n = 44)	19.5 ± 3.6	9.5 ± 3.1	<0.0001
Partial response (n = 23)	19.7 ± 4.3	13.5 ± 4.1	0.0002
Non-responders (n = 16)	19.4 ± 3.9	17.4 ± 3.9	0.92

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Introduction

Lower urinary tract (LUT) and voiding dysfunction constitute a large percentage of pediatric urology referrals, and it is estimated that daytime incontinence affects 5–7 million children 6 years of age and older in the United States [1]. A wide range of storage and voiding symptoms contribute to numerous bowel and bladder disorders [2]. Despite the generally benign nature of LUT symptoms, improved self-esteem, socialization, and independence have been observed in children undergoing bladder therapy, emphasizing the importance of prompt and appropriate management [3]. Incontinence not only has social and psychological implications, but the associated LUT dysfunction can have deleterious effects on future bladder and renal function [4,5].

Despite a multitude of treatment strategies, some children are resistant to standard therapy, with the rate of unsatisfactory response reported to be as high as one-third [6]. Children with refractory incontinence remain a time-consuming challenge, and the approach to and management of daytime wetting varies widely among programs and providers [6,7]. Imipramine is a tricyclic antidepressant (TCA) that has been shown to decrease episodes of nocturnal enuresis in patients being treated for depression, and evidence suggest that tricyclics are effective at reducing the number of enuretic episodes during treatment in the pediatric population [8]. In the current study, we assessed the impact of imipramine on treatment outcomes of children with refractory daytime incontinence, and hypothesized that daytime accidents would improve.

Materials and methods

Institutional review board approval was obtained. We reviewed the electronic medical records of 103 children treated with imipramine between 2003 and 2012. Inclusion criteria included age $\leq$18 years and refractory non-neurogenic day incontinence. Specifically, children had failed behavioral therapy, such as timed voiding, diet modification (i.e., avoidance of carbonated beverages, artificially flavored drinks, citric fruits, and caffeine) and medical therapies including bowel regimen with stool softeners and cathartics, anticholinergics, alpha-adrenergic antagonists, and desmopressin, depending on the prevailing symptomatology. Children with associated congenital malformations (i.e., ectopic ureter), neurogenic bladder dysfunction, stress incontinence, or those less than 4 years of age were excluded from the study. Children with refractory daytime urge incontinence were routinely offered imipramine therapy. Patient demographics, medical and psychiatric diagnoses, imaging, treatment, and management outcomes including side effects were abstracted.

Patients underwent a screening renal bladder ultrasound to assess for renal anomalies, urinalysis, and uroflowmetry with electromyography. Concomitant diagnoses, including constipation, were addressed. Imipramine was initially started at 10 mg and increased as needed to 2–3 mg/kg/day, with a maximum dose of 75 mg/day. Primary endpoint was resolution of incontinence. Treatment success was defined as per the International Children's Continence Society (ICCS) [2,9]. The Vancouver Symptom Score was completed at initial consultation and each subsequent clinic visit after 2009 and the scoring was done retrospectively on visits before 2009 [10]. Pre-treatment VSS was recorded prior to initiating imipramine, but after implementation of a bladder–bowel regimen and/or standard pharmacotherapy. The questionnaire was self-administered and completed by patients and/or parents. Response to imipramine, and the duration of time to endpoint, were determined. Response to imipramine was measured using the ICCS criteria as follows: 1 was assigned to patients who demonstrated full resolution of symptoms, 2 partial relief (50%–99% decrease in symptoms), 3 non-response 50% or less response, 4 denoted patients lost to follow up, and 5 was assigned to those that discontinued imipramine because of side effects. Children with a complete response were tapered off at 3 months and therapy resumed if symptoms recurred. Chi-square and one-way Anova with the Bonferroni correction were used to perform intergroup analysis. The Student *t* test was employed to compare patient characteristics to treatment outcome. Statistical analysis was performed using XLStat and StatPLus, with $p < 0.05$ representing statistical significance and all associated confidence intervals equal to 95%.

Results

One hundred and three patients (55 males, 48 females) with refractory urinary incontinence were treated with imipramine during the study period. Patient enrollment by calendar year starting in 2003 and ending in 2012 was 5, 3, 4, 18, 20, 10, 13, 7, 10, and 13. Of these, 101 were diagnosed with urge incontinence and two had giggle incontinence. Mean age at diagnosis was 11.2 years (95% CI 10.2–12.3) and average length of follow-up on imipramine was 13.1 months (95% CI 8.2–17.9). Males were slightly older than female patients (11.2 years 95% CI 8.9–13.5 vs. 10.3 95% CI 9.1–13.4). At the last follow-up, 42.7% of children ($n = 44$) had complete treatment response, 22.3% ($n = 23$) had partial response, and 15.6% ($n = 16$) were classified as non-responders. There was no significant difference in age between response groups (Table 1). Children who discontinued imipramine due to side effects were included in the nonresponse group. Seventeen children (16.5%) were lost to follow-up and three refused treatment (2.9%). The mean total follow-up was 20.5 months (95% CI 12.7–28.4).

Pre- and post-treatment VSS were statistically different in both complete and partial response groups (complete 19.5–9.5; $p < 0.0001$ and partial 19.7 to 13.5; $p = 0.0002$); in the non-responders there was no difference noted pre- and post treatment (Table 1). Side effects were reported by 11 out of 83 (13.3%) patients; partial responders experienced a significantly higher likelihood of side effects (26.1%; $p = 0.03$). Significant side effects included suicidal thoughts in one child while three reported mood changes, including irritability and anger. Other reported side effects included headaches in three children, tic like behavior in one, and fatigue in one patient.

Mean maximal dose in the 83 patients with follow-up was 30.2 mg (95% CI 22–48.8). There was a trend for children

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