



Primary Nocturnal Enuresis: A Novel Therapeutic Strategy With Higher Efficacy

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OBJECTIVE	To introduce a new protocol for patients with primary nocturnal enuresis to increase efficacy of treatment and decrease relapse rate.
METHODS	A prospective study was done on 185 children diagnosed with nocturnal enuresis between the years 2007 and 2014. Inclusion criteria consisted of age > 5 years, monosymptomatic enuresis or non-monosymptomatic enuresis, strict abidance by the protocol, and follow-up > 24 months. Exclusion criteria consisted of secondary enuresis, poor compliance to protocol, and neurogenic bladder. Participants were started on combination therapy of desmopressin 120 µg (MELT formula) once per day and propiverine 7.5 mg twice per day, which were then adjusted as per their response to therapy and our designed protocol. Outcome was defined as per the International Children Continence Society (ICCS) latest definitions.
RESULTS	One hundred twenty-two patients satisfied the inclusion criteria and were included in the study with a median age of 9 years (range 5-19 years). The mean follow-up time was 62 months (range 25-114 months). Our protocol showed an overall complete success of 87% with failure and relapse of 13%. The success rate of patients needing 120 µg desmopressin as maintenance therapy to achieve dryness was 92.7% as compared to 65% success in patients needing a higher dose of desmopressin to achieve dryness ($P < .05$). Age, gender, and type of primary nocturnal enuresis had no effect over success (all $P > .05$).
CONCLUSION	Adopting combination therapy along with structured withdrawal as per our protocol showed higher success rates and lower relapses in primary nocturnal enuretic children. UROLOGY 124: 241–247, 2019. © 2018 Elsevier Inc.

According to the International Children's Continence Society (ICCS), enuresis is defined as a symptom and a condition of intermittent incontinence that occurs during periods of sleep among children aged more than 5 years with > 1 episode per month, and a frequency of 3 episodes over 3 months.¹ The effect of enuresis on the psychology and social status of the child makes its treatment more important.² Prevalence of enuresis varies among age where 15% of children will have enuresis at the age of 5 with spontaneous resolution of 15% per year.³

Enuresis is divided into two subtypes: monosymptomatic enuresis (MSE) and non-monosymptomatic enuresis (NMSE). The difference is that children with MSE suffer solely from enuresis without any lower urinary tract symptom (LUT), excluding nocturia, whereas children with NMSE have at least one LUT symptom during daytime.¹

The pathophysiology of enuresis is complex involving mainly 3 systems, the bladder (reduced functional nocturnal bladder capacity), the kidney (nocturnal polyuria), and the brain (disorder affecting arousal from sleep).⁴ Hence, genetics, sleep disturbances, maturational delay, and abnormal secretion of antidiuretic hormone all seem to play a role in its development.⁴ The complexity of enuresis makes its approach and treatment more challenging to the physician.

Desmopressin, a synthetic analog of arginine vasopressin (ADH), released by the posterior pituitary gland reduces urine production by increasing water reabsorption by the collecting tubules. It is considered the first-line therapy for MSE.⁵ Almost 30% of children with enuresis show full response and 40% have a partial response,⁶ whereas the relapse rate after discontinuation is high (60%-70%).⁷

Propiverine hydrochloride (referred to in the following as propiverine) is a benzylic acid derivative that has neurotropic and muscolotropic effects on the urinary bladder.⁸

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Propiverine's bioavailability does not depend on food intake and its affinity to muscarinic receptors was demonstrated with significantly lower affinity for cardiac M2 receptors. The efficacy and safety profile of propiverine has been established in the children population with better tolerability as compared to oxybutynin.^{9,10}

Initial treatment of enuresis has been established through guidelines but the strategy by which treatment is terminated has not been fixed yet with rates of relapse still considerably high.

The rationale behind establishing a new protocol for primary nocturnal enuresis is as follows:

- Observation that daytime symptoms are largely under reported, explaining the low initial response to desmopressin.
- Strong belief that we cannot treat a developmental impairment with a short treatment regimen and even less by stopping the therapy abruptly.
- The disappointing results of known treatment strategies, with response rate (31%-75%) and relapse rate (48%-82%).⁶

The aim of the current study is to introduce a new protocol including a combination therapy of desmopressin with propiverine along with a structured withdrawal regimen to tackle both MSE and NMSE and hence decrease the relapse rate accompanying monotherapy or sudden withdrawal of therapy.

MATERIALS AND METHODS

Between 2007 and 2014, a total of 185 patients presented to our clinic with the diagnosis of enuresis. Patients were followed up in the clinic and a closing phone call was made to all of them in February 2017.

We defined our inclusion criteria as follows: age > 5 years, MSE and NMSE patients, strict abstinence by the protocol, and follow-up period of at least 24 months.

Our exclusion criteria were as follows: secondary enuresis, neurogenic bladder, post void residue more than 20%, and poor compliance to protocol.

Sixty-three patients of the total 185 patients were eliminated from the study as they follow the exclusion criteria: 6 patients were initially excluded because of secondary enuresis (children who developed enuresis after a dry period of at least 6 months¹), 5 patients with neurogenic bladder, and 7 with post void residual more than 20%. Fourteen patients were lately excluded from final analysis due to lack of compliance and 31 were lost to follow-up.

After exclusion, 122 enuretic patients were prospectively enrolled and completed the study. Patients were received in the clinic where a thorough detailed history and physical examination were performed. Patients and their parents were interviewed for all related symptoms of enuresis and lower urinary tract symptoms. All patients were requested a urinalysis, and an ultrasound in those with major daytime symptoms.

In children, the recommended average daily dose of propiverine is 0.8 mg/kg and an initial higher dosage corresponded to improved efficacy reflected in higher continence rate.⁹ In the current study, an arbitrary dose of propiverine (7.5 mg twice a

day) along with desmopressin was given to enrolled patients starting the protocol.

The adopted protocol, as depicted in Figure 1, required the patients to start the combination therapy: 1 tablet desmopressin 120 µg (Minirin Melt) once per day (qd) and propiverine 7.5 mg twice per day (bid) for 3 months (step 1: initiation of treatment). The parents were instructed to give desmopressin at bedtime, and all the children were advised to empty the bladder and restrict fluid intake 3 hours before going to bed.

The second step consisted of finding the maintenance dose where the child is assessed at 2 weeks and in case of complete response, or high partial response, the protocol was continued as started (desmopressin 120 µg and propiverine 7.5 mg bid) for 3 months. In case of failure, the desmopressin dose is gradually increased to 180 µg and then to 240 µg in 2-week intervals until reaching a clinical response. If no response was documented even on 240 µg desmopressin along with propiverine 7.5 mg bid, the child is eliminated from the study, and failure of therapy documented. The child is maintained for 3 months at the dose of desmopressin that provides complete response.

The third step of the protocol consisted of the withdrawal strategy: dropping 60 µg of desmopressin at each level (per month), if the child was still demonstrating complete or partial response (< 3 enuretic episodes per month) while keeping propiverine dose of 7.5 mg bid, until the dose of desmopressin reaches 60 µg qd. Desmopressin 60 µg is then given every other day (QOD) along with propiverine for 1 month before stopping desmopressin completely.

The patient would stay on propiverine 7.5 mg bid for 1 month afterward, and then finally on propiverine 7.5 mg HS for another month before stopping the treatment completely. The protocol would only be progressed if the patient was demonstrating response; if not, the patient would repeat the month where he demonstrated response before progressing further in the withdrawal strategy.

In case of complete response, the treatment would be stopped, and by then the patient would have achieved complete dryness with full success.

This study adhered to the recent ICCS terminology: Initial success indicates reduction of episodes in less than 50%, partial response denotes a reduction of symptoms from 50% to 99%, and complete response designates 100% reduction.¹

Concerning the long-term success, it is divided into 3 phases: relapse phase—more than one symptom recurrence per month; continued success phase—no relapse in 6 months after interruption of treatment; and complete success phase—no relapse in 2 years after interruption of treatment.¹

Statistical analysis was performed by SPSS, version 22. Chi-square, ANOVA, and *t* test were used to identify the correlation between variables. Statistical significance was represented by a *P* value of .05.

RESULTS

One hundred twenty-two patients were included in the study: 63% were male and 37% were female. The median age was 9 years (range 5-19 years). 82.8% of the population had non-monosymptomatic enuresis with 65.3% males and 34.6% females. As for the monosymptomatic type, they constituted 17.2% of our patients with 52.3% males and 47.6% females. Forty-nine percent of our patients had previous therapy before enrolling in our protocol guided study. Therapies included

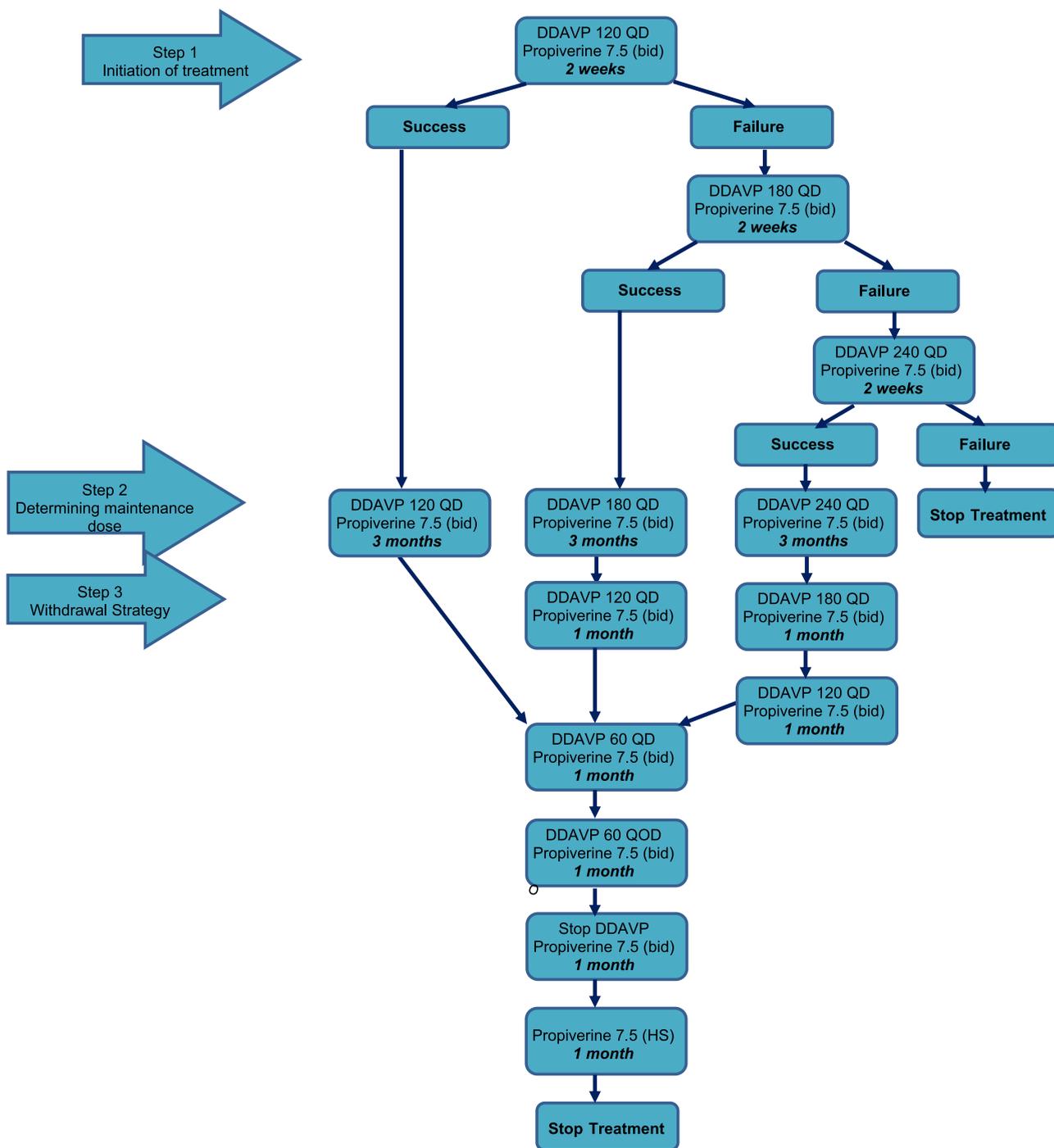


Figure 1. The protocol used in our study depicting the combination therapy used with the structured withdrawal strategy (DDAVP: desmopressin; QD: once daily; bid: twice a day; HS: at bedtime). (Color version available online.)

antidepressant (imipramine, which is a tricyclic antidepressant used previously for the treatment of enuresis), anticholinergics, and desmopressin. Forty percent of those children took as prior therapy a combination of desmopressin and anticholinergic and stopped abruptly. As for the follow-up time of those patients, it started from the first day the patient started therapy, until the date we contacted them to check if they achieved complete response or relapsed again. The follow-up period extended from 25 to 114 months with a mean follow-up time of 62 months.

Results showed 86.9% overall success of the protocol: 66.4% had immediate response with no relapse during the 7-month

protocol, 15.6% relapsed at least once during their treatment but ended up succeeding by abiding to the protocol, and 4.9% relapsed multiple times after finishing their 7-month treatment within a period less than 24 months post therapy and had to take the whole protocol again in order to succeed. As for the rest of the population, 13.1% didn't achieve dryness after multiple attempts even on higher dosage on a follow-up period of at least 2 years and were considered as failure of therapy (Fig. 2).

The mean age of the population whether the patients failed or succeed was 10 years. There was no significant relation between age range and success ($P = .5$).

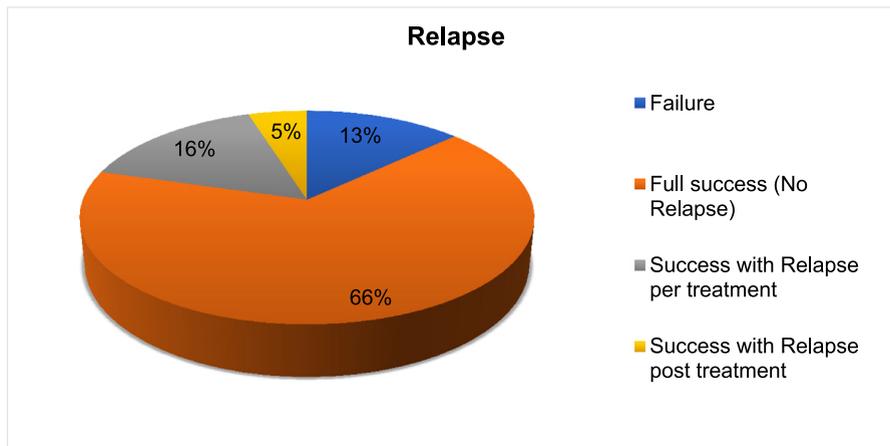


Figure 2. Chart showing percentage of full success, success with relapse per treatment, success with relapse post treatment, and failure. (Color version available online.)

Regarding the gender, 91% of the female population achieved complete response with an 84% in the male population. These results turned to have no significant statistical influence ($P = .2$).

Knowing that most of our patients had non-monosymptomatic enuresis, still the success rate between the two types of enuresis was approximately the same, with 87.1% overall success in NMSE and 85.7% in MSE. There was no significant difference between the type of enuresis and the success rate ($P = .8$).

As mentioned before, 49% of the sample took prior therapy and 51% didn't. Statistically, there was no significant relation whether the patient took prior therapy (86.7% success) or not (87.1%) with a P value of .9.

As per our protocol, the desmopressin dose required for maintenance for the first 3 months is 120 μg . The initial dose of desmopressin to achieve dryness 120 μg or more was associated with a significantly different success rate. Those needing more than 120 μg had a higher risk of failure. The success rate of the population who took desmopressin 120 μg for 3 months as maintenance dose was 92.7%, whereas the patients who took higher maintenance doses had a success rate of 65.3% ($P = .003$) (Table 1).

As for the patients who did not abide by our protocol and stopped their treatment abruptly, they had a 100% rate of relapse. Those patients were excluded since they did not fulfill the inclusion criteria set for our study.

DISCUSSION

It has been well established that desmopressin is the first-line therapy for enuresis with moderately high efficacy rates but with the disadvantage of high relapse of

symptoms after stoppage. Studies have been performed showing better results with structured withdrawal of desmopressin, but there has been no consensus in the literature on how to stop desmopressin. Structured withdrawal strategies mainly consist of either time dependent (increasing time interval with maintaining the same dosage) or dose dependent (decreasing the dose of desmopressin with fixed time interval). The protocol in this article outlines a combination therapy with a structured withdrawal strategy being both time and dose dependent.

Patients enrolled in this study were mostly referred to us either from pediatricians or from general practitioners. Most of the patients referred were labeled to have monosymptomatic enuresis, but with detailed history upon presentation, many were found to have daytime symptoms and were hence classified as non-monosymptomatic enuresis. Parents of enuretic children are solely bothered by the enuresis and its impact on the social and psychological status of the child, and hence neglect or fail to report the daytime symptoms. Enuresis has a complex pathophysiology with multiple systems involved, and with the current relapse rates described in the literature it all led us to combine MSE and NMSE patients to take the same protocol based on a combination therapy of desmopressin and anticholinergic, along with a well-defined structured withdrawal regimen, and start a prospective study after a trial period that showed us promising results. In our study, 83% of patients were classified as NMSE

Table 1. Success of therapy in term of maintenance dose of desmopressin

Maintenance dose	Desmopressin 120 μg (for 3 months)	Outcome				Total	P
		Failure	Full Success	Relapse per TRT	Relapse Post TRT		
		7	67	17	5	96	.003
		7.3%	69.8%	17.7%	5.2%	100.0%	
	Others	9	14	2	1	26	100.0%
		34.6%	53.8%	7.7%	3.8%	100.0%	
Total		16	81	19	6	122	100.0%
		13.1%	66.4%	15.6%	4.9%	100.0%	

Table 2. Comparative table of previous published data

Reference	Type of Enuresis	N	Drug	Treatment Duration	Follow-up Period	Success	Relapse Rate
Aladjem ¹¹	MSE and NMSE	32	10 µg i.n. DDAVP	30 days	30 days	High	High
Austin ¹²	MSE	41	0.6 mg DDAVP vs DDAVP + Ach PO	30 days	n.a.	66%	n.a.
Chiozza ¹³	MSE	237	20-40 µg i.n. DDAVP	6 weeks	n.a.	75%	n.a.
Monda ¹⁴	MSE	88	20 µg i.n. DDAVP	6 months	6 months	68%	82.30%
Birkasova ¹⁵	NMSE	22	10-40 µg i.n. DDAVP	2 weeks	1 month	68%	56%
Ferrie ¹⁶	NMSE	22	20 µg i.n. DDAVP	2 weeks	n.a.	31.80%	n.a.
Fai-Ngo Ng ¹⁷	MSE	38	0.4 mg PO DDAVP	12 weeks	12 weeks	52%	60%
Fjellestad-Paulsen ¹⁸	MSE and NMSE	30	0.2 mg PO vs 20 µg i.n. DDAVP	6 weeks	1 week	41%-52%	69%
Post ¹⁹	MSE, NMSE, and secondary enuresis	52	40 µg i.n. DDAVP	2 weeks	3 months	75%	81%
Ferrara ²⁰	MSE	81	120 µg DDAVP MELT	3 months	1 month	58%	46%-48%
Fera ²¹	MSE	15	0.2-0.4 mg DDAVP PO	30 days	30 days	34.30%	n.a.
Snajderova ²²	MSE	55	7-21 µg DDAVP i.n.	6 months	42 months	61%	30%
Gokce ²³	MSE	195	120-240 µg DDAVP MELT	14 weeks	12 weeks	–	39%-55%
Our results	MSE and NMSE	122	60-240 µg MELT DDAVP + propiverine	7-15 months	25-114 months	86.90%	13%

Ach, anti-cholinergic; DDAVP, desmopressin; i.n., intranasal; MSE, monosymptomatic enuresis; N, sample size; NMSE, non-monosymptomatic enuresis; n.a., not assessed.

with 13% classified as MSE; both were combined and were started on our described protocol.

A multicenter study compared the use of desmopressin alone versus its combination with propiverine 10 mg for the treatment of MSE; it showed clear superiority of the combination therapy group in terms of success of therapy.²⁴ Another case series also demonstrated the superiority of combination therapy (desmopressin with propiverine) over desmopressin therapy alone. In this case, series propiverine dose was 15 mg/day if patient was < 30 kg and 20 mg if patient was > 30 kg.²⁵ Propiverine pharmacokinetics showed advantage of 2 daily dosing instead of single dosing in terms of bioavailability and plasma concentration in the children population.²⁶ In the current study, a dose of 7.5 mg of propiverine twice a day was selected for starting the protocol to render it independent of the patient's weight where 15 mg/day is going always to be less than the maximal dose allowed for children and for the advantage of twice dosing.

There have been many studies published previously on desmopressin showing its efficacy but as shown in our table, the main issue in the desmopressin treatment remains the high relapse rates after its cessation. Other studies have advocated for the structured withdrawal of desmopressin, yet only a few with the fast melting oral formulation of desmopressin that is currently the standard formulation. The desmopressin formulation (MELT) has been shown to have similar levels of efficacy and safety at lower dosing level since its bioavailability is almost 60% greater than that observed for the tablet formulation.²⁷ This increase in bioavailability is also related to lower food interaction, permitting the child to take the drug nearer to the last meal and increasing compliance.²⁸ Our protocol was based on the structured withdrawal of this new oral

formulation of desmopressin (MELT) and is one of the few described articles using this oral formulation.

The studies cited in our table all had a high success rate, yet the relapse rate was high as well ranging from 30% to 82%. In a study conducted in Italy by Ferrara et al, the abrupt cessation of the fast melting oral formulation of desmopressin was compared to a single withdrawal program of 60 µg desmopressin daily for 15 days and then 60 µg every second evening for another 15 days; the relapse rate was as high as 47% in the structured withdrawal group. The follow-up time in this study was 4 weeks and it did not show any superiority of the structured withdrawal to the abrupt cessation.²⁰

A multicenter randomized control trial in Turkey by Gökçe et al proved the superiority of structured withdrawal in comparison to abrupt stopping of the fast melting oral formulation of desmopressin, with improvement in relapse rates (39% and 42%) as compared to 55.3% in the abrupt stoppage group.²³ This study had a 12-week follow-up period after initiating treatment and hence the patients were not assessed for relapse on the long term.

Our study is a prospective study, with 122 eligible individuals included, all abiding by our protocol. All patients who were lost to follow-up or did not strictly abide by our protocol or follow-up schedule were excluded. We had a long follow-up period of at least 2 years (mean 62 months) and hence we abided by the ICCS terminology as the patients who succeeded the protocol and did not relapse can be considered in the complete success phase (no relapse after 2 years of interruption of treatment).¹ The long follow-up duration imposed by our protocol led to considerable number of dropouts and lost follow-up in a substantial portion of recruited patients.

Our results have shown that 100% of the patients who did not abide by our protocol and stopped their treatment

abruptly after a dry period relapsed compared to a 13% relapse rate for those who abided by the protocol. Sixty-six percent needed only the minimum time required by our protocol and demonstrated complete success, whereas 21% needed higher dosage or more time to reach the full success phase. Our overall complete success after follow-up on all the patients included was as high as 87% with only 13% failures and relapse over the whole period of our study.

Our secondary outcome measures were to identify any factors affecting success or failure. The gender, age, type of enuresis (MSE or NMSE), and whether the patient had prior therapy all did not affect the outcome of success or failure with a *P* value of $> .5$, while the maintenance dose required had a statistically significant effect and hence can predict the eventual success of treatment (Table 2). This adds to the complexity of enuresis by itself but renders our protocol more convenient as it can be applied to the various categories of patients with the same outcome.

A structured withdrawal program may impose a prolongation of treatment in children who already had a response to therapy, and this may affect the compliance of the patient and parents to treatment. A large number of exclusions in our study were mainly due to the noncompliance and the lost follow-up of the patients. With the high relapse rates that abrupt desmopressin stoppage is demonstrating, it is crucial though to insist on a plan and to rely on a protocol to gradually withdraw the medications for the patient to continue demonstrating the effect of therapy. Our protocol showed promising results, but the greater number and the presence of a placebo group would increase the strength of our results.

CONCLUSION

In conclusion, we presented a novel therapeutic strategy consisting of a combination therapy along with a structured withdrawal regimen being both time and dose dependent and a long follow-up period showing better efficacy and less relapse rates in the treatment of primary nocturnal enuresis.

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