

Treatment Modalities of Nocturnal Enuresis: Recent Recommendations

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Abstract:

Background: Enuresis is a clinical condition with a multifactorial etiology that generates great impacts on social relationships, self-esteem, family relationships, and even the academic life of children and adolescents with nocturnal enuresis. The pathogenesis of this condition is understood through three mechanisms: high thresholds for arousal to full bladder signs, nocturnal polyuria, and nocturnal detrusor hyperactivity. Three conditions are felt to contribute to nocturnal enuresis; impaired sleep arousal threshold, nocturnal polyuria and detrusor over activity. This knowledge helps the practitioner understand the different treatment modalities available for their enuretic patient. Importantly, experts recognize that a significant portion of monosymptomatic enuresis patients likely have underreported or underdiagnosed daytime symptoms, thus explaining the overlapping therapeutic efficacy in many patients. The mainstay of treatment is urotherapy with information and psychoeducation about normal lower urinary tract function, the underlying cause of MEN, disturbed bladder dysfunction in the child with NMEN and instructions about therapeutic strategies. Alarm therapy and the use of desmopressin have been shown to be effective in randomized trials. Children with NMEN first need treatment of the underlying daytime functional bladder problem before treatment of nocturnal enuresis. In patients with findings of overactive bladder, besides urotherapy, anticholinergic drugs may be useful.

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Introduction:

Nocturnal enuresis (NE), or simply enuresis, is a common childhood problem. It is observed in 10% of children at the age of 7 years, 3.1% at 11–12 years, and 0.5–1.7% at 16–17 years. It is

seen more frequently in boys. The prevalence of enuresis decreases by about 15% with each year. Enuresis is often highly distressing for children and parents and in many cases, the quality of family life is affected. Loss of self-esteem, social isolation, poor school performance, and psychological impairment, in addition to domestic violence, have been described.

The estimated prevalence of NE is highly variable depending on the geographical areas involved, the composition of the population studied and the diagnostic criteria. (1).

The general rate of clinically relevant behavioral disorders (anxiety, anorexia nervosa, autism and depressive disorders) in children and adolescents lies between 10% and 15%. The rate of comorbid psychological disorders is increased in children with all types of incontinence (2).

Prevalence of nocturnal enuresis in Egypt

A study carried out in Assiut city, Egypt, they reported a prevalence rate of 17.8% among children of 5-12 years old joining a primary governorate school. (3)

A cross-sectional comparative study that was conducted on 723 students aged 6-18 years in Menoufia governorate showed that Prevalence of NE was 11.5 % with significantly associated positive family history, however secondary type was 3.2% (4)

In a cross-sectional study conducted on 450 students aged 6–12 years in Qalubia governorate, the prevalence of NE was 15.7 %, where PMNE was 67.1%, and the secondary enuresis was 32.9%. Positive family history was 30% among the involved students (5).

While in a case–control study conducted during the academic year 2013/2014 on 325 students aged 6–12 years in Damietta governorate, the prevalence of NE was 15.4%. (6).

In a cross-sectional study conducted on school-age children from two governorates in south of Egypt, they found that, of 4652 students, 834 (18 %) had NE, with no significant difference between rural and urban areas (17.5 vs. 18.4 %, $p = 0.4$). Younger age categories showed higher prevalence of MNE than in older children (7).

Three conditions are felt to contribute to nocturnal enuresis; impaired sleep arousal threshold, nocturnal polyuria and detrusor over activity. This knowledge helps the practitioner understand the different treatment modalities available for their enuretic patient. Importantly, experts recognize that a significant portion of monosymptomatic enuresis patients likely have underreported or underdiagnosed daytime symptoms, thus explaining the overlapping therapeutic efficacy in many patients (8).

When first presented with an enuretic patient, education and simple behavior maneuvers should be employed. Patients should be educated about normal bladder function and be instructed to void regularly throughout the day, immediately before bedtime, and on awakening. Bladder retention training (The majority of fluid intake should occur throughout the morning and afternoon with minimal drinking in the evening hours), reduce the number of voids during the day and interrupt voiding (stop start training) (9).

Other simple measures such as reward systems for dry nights can be instituted. Compared to controls, children who underwent behavioral therapies were found to have fewer wet nights and

lower relapse rates. However, both the response and relapse rate are inferior compared to enuresis alarms and drug therapy (10).

A positive attitude towards the child should be utilized and explaining that bedwetting will eventually cease—but nobody knows exactly when, reassurance to the parents and encouragement to the child. After excluding underlying medical conditions and relevant comorbid conditions, the ICCS recommends a stepwise approach to treatment of monosymptomatic enuresis. Prior to instituting any urotherapy, the practitioner should assess and treat constipation and oxyuria. The family should assess nocturnal urine production by weighing diapers and measuring voided volumes during normal feeding and drinking. When present, nocturnal polyuria, defined as urine volumes greater than 130% of expected bladder capacity for age, can help direct the practitioner towards desmopressin therapy (1).

*** *Motivational and Behavioral Therapy***

Motivational therapy appears to be a reasonable first line. It is used to eliminate nocturnal enuresis and involves reassuring the parent and the child, removing the guilt associated with bedwetting, and providing emotional support to the child. Emphasis should be placed on the child to take responsibility for bed-wetting by explaining the condition, reinforcing the fact that he/she did not cause the problem.

It is important to emphasize to parents that many children with occasional daytime incontinence or enuresis will fall within the normal developmental spectrum, and that their children status is expected to improve over time (11).

The management of the bladder can begin after a bowel management program, when indicated, has resulted in regular soft daily bowel movements. Behavioral therapy is a good starting point, the hallmark being the institution of a strict every 2–3 h daytime voiding regimen after educating the child about normal bladder function and sensation. Children are also encouraged to avoid caffeinated, carbonated, and highly acidic fluids. Information regarding the time and the amount of each void and/or leakage episode, time and consistency of each bowel movement, and amount of fluid intake should have included. The goal of behavioral therapy is to reeducate the child about normal bladder sensation and garner central control to suppress bladder urges (12).

Rewards for complying with procedures and for self-monitoring wet and dry nights should be included in the treatment of young children. Parental support and negative patient perceptions of bed-wetting favor positive outcomes. In addition, children should participate in cleanup of bed linens and soiled laundry whenever possible. This should not be viewed as punitive, but as a consequence of the problem. This involvement may be viewed as undesirable by the child and, in turn, become a motivating factor in staying dry (13).

Complementing behavioral therapy is biofeedback therapy, which provides visual and auditory feedback to children about the external urethral sphincter and pelvic floor bioactivity during bladder filling and emptying. Programs and games integrated with pelvic floor rehabilitation are then used to teach children how to respond to normal bladder urges during

storage and promote pelvic floor relaxation during bladder and bowel elimination, thus targeting detrusor over activity and dysfunctional voiding, respectively (14).

Although there are no randomized controlled trials assessing the efficacy of biofeedback therapy, one observational study showed improvement in 89% and 90% of children with daytime incontinence and nocturnal enuresis. Constipation was improved in 100% and resolved completely in 33%. While behavioral and biofeedback therapy are good non-invasive, non-pharmacologic methods to treat urinary incontinence, pharmacologic therapy plays an important role in pediatric voiding dysfunction, particularly among patients who do not respond to conservative approaches (14).

Enuresis alarm

The enuresis alarm is the most effective means of facilitating arousal from sleep and remains an effective way to treat MNE in those who do not respond to education and simple behavior maneuvers. It is slow in the beginning so it should be continued at least 6 to 8 weeks before it is considered effective or not. Compliance remains a problem (15).

Alarm is Placed under the bed linens or applied to the undergarments, the alarm senses wetness and arouses the patient with an audible or vibratory alarm. Nearly two-thirds of patients become dry while using the alarm, thus making it an excellent therapeutic option. Of those who become dry on therapy, nearly half will relapse. Overlearning is the process whereby newly dry patients are given extra fluids prior to bedtime while still using the device, and has been shown to lower relapse rates. An interesting finding is that the alarm increases nocturnal bladder capacity, which may explain why children after successful treatment are often able to sleep dry without nocturia. Usage of bed wetting alarm in treatment of patients with MNE is effective. However patients response is also affected by other possible risk factors (age, behavioral treatment, presence of constipation, punishment and family troubles) while other risk factors were found to have minimal effects as sex, family history, family education and residence. Success was achieved in 68% of children (16).

a. Arousal training

Arousal training entails reinforcing rapid appropriate behavior [waking and toileting] in response to alarm triggering, not only learning to keep the bed dry ‘.

The instructions involve:

- Setting up the alarm before sleep.
- When the alarm is triggered the child must respond by turning it off within 3 minutes.
- The child completes voiding in the toilet, returns to bed and re-sets the alarm.
- When the child reacts in this fashion he is rewarded with 2 stickers
- When the child fails to respond in this way the child pays back one sticker.

Van Londen. (17). first described this procedure with a group of 41 children, aged 6-12 years, with predominantly primary enuresis. They reported 98 percent success (14 consecutive dry nights) compared to 73 percent success with alarm monotherapy (17).

b. Dry bed training

It incorporates:

- The enuresis alarm - Positive practice (practice of waking),
- Cleanliness training (encouraging the child to take responsibility for removing of wet night clothes and sheets, re-making the bed and resetting the alarm),
- Waking schedules - Social reinforcement
- Decrease night fluid intake, (10).

REVIEW OF LITERATURE

Waking schedules involve:

For the first night, waking the child each hour, praising a dry bed, encouraging the child to decide at the toilet door whether he or she needed to void, and on returning to bed the child is encouraged to have a further drink and on the second night the child is woken and taken to the toilet 3 hours after going to sleep. For each dry night the waking time is brought forward by 30 minutes, if wet on any night, the waking time stays at the time of the previous evening. The waking schedule was discontinued when the waking time reached 30 minutes following sleep. The waking schedule is resumed if the child begins wetting twice or more in any week, stating again 3 hours after sleep (18).

High success rates and low drop out have been reported although relapse rates are no different to enuresis alarm treatment. Modifications have been advocated to remove some of the more punitive elements of the program but it remains a complex and time consuming (10).

*** *Psychological treatments for the management of bedwetting***

Bedwetting itself may be a source of low self-esteem and bedwetting has been associated with emotional and behavioral disorders. Psychological treatments might be of benefit to the management of emotional or behavioral problems in their own and hence to the management of the bedwetting itself. When patients were admitted to physicians for treatment, trust should be provided for children and families and the necessary psychological support should be provided jointly by child psychiatrists and psychologists (19).

*** *Pharmacological Treatment***

The outcome of pharmacological treatment for nocturnal enuresis is expressed as either full response or partial response, while on the prescribed medication. A full response is defined as a reduction in wet nights of at least 90%, to allow for the occasional 'accident of wetting', partial response is defined as a reduction in wet nights of 50%-90%; less than 50% reduction in wet nights is considered to be non-response. A lasting cure is defined as a full response still present 6 months or longer after discontinuation of pharmacotherapy (20).

1- Desmopressin:

Desmopressin is a vasopressin analogue with an antidiuretic effect. In most children levels of ADH rise overnight and prevent as much water being excreted by the kidneys as during the day. This causes urine to become concentrated in a smaller volume overnight which allows the majority of children to sleep through the night without needing to pass urine. In some children this mechanism is late to become established and they continue to produce large volumes of dilute urine overnight, resulting in a full bladder and either needing to get up to pass urine or if they fail to wake; they will wet the bed (10).

The ICCS suggest that the best candidates for this therapy are those with nocturnal urine production > 130% of expected bladder capacity for age (nocturnal polyuria). While actively taking the medication, 30 and 40% of children are estimated to be full and partial responders, respectively (1).

Desmopressin should be avoided in children who have fluid control problems such as in heart failure and should be carefully considered if children are likely to find difficulty complying with the fluid restriction requirements, for fear of hyponatremia-related seizure (21).

2- Anticholinergic medication

Anticholinergic medicine reduces the number of involuntary bladder contractions and also has a relaxant effect on the smooth muscle of the bladder so allows the bladder to hold more urine. Both M2 and M3 muscarinic receptors are found in the bladder, but the M3 subtype stimulation results in direct detrusor contraction and micturition. In blocking these receptors, anticholinergics mitigate the impact of uninhibited bladder contractions and increase bladder capacity, thereby decreasing incontinence episodes and increasing the time between and volume of each voiding episode. (22)

In general anticholinergics are very safe and in low doses are less likely to have side effects. The side effects of anticholinergic drugs include dry mouth, blurred vision, facial flushing, headache, tiredness, gastrointestinal discomfort, constipation, retention of urine and very occasionally unusual behavior or night terrors. The degree to which these side effects are apparent depends on the specificity of the selected anticholinergic. Oxybutynin is known to decrease sweating, thus causing heat intolerance and overheating during the summer as well as preventing some athletes from tolerating this drug while engaged in sport. All these side effects resolve when medication is stopped. Patients with concomitant constipation should be thoroughly evaluated and maintained on an effective bowel regimen before initiating anticholinergic therapy. There are few randomized controlled trials assessing the efficacy of oral anticholinergics in children with daytime incontinence (17).

In those children who have NE due to detrusor over activity during the night, treatment with an antimuscarinic drug should be considered. Because it is difficult to perform a night time cystometry in these children it may be tried in children who have more than 2 wetting episodes per night and who do not respond to desmopressin or be given in combination with alarm or desmopressin (23).

3- Tricyclic medication and the management of bedwetting

Of the tricyclic antidepressants (TCA), imipramine is historically the most commonly used in enuresis treatment. In addition to its peripheral anticholinergic effects, it acts centrally to increase vasopressin release and modify the sleep arousal pattern. To minimize side effects it is best started as a low dose and increased fortnightly to the maximum dose allowed for the age of the child (10).

For enuresis, the doses (given around 3 hours before sleep) are 25 mg for patients younger and 50 mg for patients older than 9 years. Side effects of imipramine include typical anticholinergic effects such as dry mouth and constipation. Mood changes and insomnia have been reported in children taking it for enuresis (20).

At high doses, imipramine is cardiotoxic, so its use in those with long QT syndrome or a family history of sudden cardiac death should be avoided. Therapy should be interrupted every three months to avoid tachyphylaxis. Although the side effect profile favors desmopressin, the lower cost of imipramine may make it more attractive to some families (24).

If offering imipramine for bedwetting, inform the parents that many children, but not all, will experience a reduction in wetness, the dose should be increased gradually, the initial treatment course is for 3 months and further courses may be considered, the particular dangers of imipramine overdose and withdraw imipramine gradually when stopping treatment for bedwetting (12).

4- Inhibitors of prostaglandin

Because nocturnal polyuria in children with nocturnal enuresis may not be entirely attributed to a defect in free water excretion, but rather to an increase in nocturnal excretion of sodium, cyclooxygenase inhibitors (like diclofenac), which reduce urinary sodium excretion, have been tried and in a randomized double blind placebo controlled study proved to be effective. Further studies need to be done to elucidate the role of these drugs (25).

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