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Advances in Treatment of Nocturnal Enuresis in Children

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Abstract

Nocturnal enuresis is a condition with complex etiology affecting plenty of children and families. Even though multifarious clinical trials and studies have been designed and completed, some inconclusive results on nocturnal enuresis confuse clinicians. This article aims to provide useful information for clinicians by summarizing the existing evidence on nocturnal enuresis and discussing the effectiveness and safety of different treatments. Nocturnal enuresis mainly results from the disorders related to central nervous system, which may cause nocturnal polyuria, nighttime bladder capacity decline, arousal disorder, and various accompanying diseases. We discussed the efficacy and safety of different treatments for monosymptomatic nocturnal enuresis, including standard therapies, simple behavioral interventions, complex behavioral interventions, alarm therapy, desmopressin and other drugs, biofeedback therapy, electrical stimulation, acupuncture, Chinese herbal medicine, massage, and so on. Alarm is still the most effective single therapy with lower relapse rate. Desmopressin has efficacy mainly in children with nocturnal polyuria. Children with detrusor overactivity or decreasing functional bladder capacity can choose anticholinergics. Additionally, tricyclic drugs, biofeedback therapy, electrical stimulation, acupuncture, massage, and so on are therapeutic options for children with nocturnal enuresis.

Keywords: nocturnal enuresis, alarm, desmopressin, behavioral interventions, acupuncture

1. Introduction

Nocturnal enuresis (NE) is a common disease that pediatricians often encounter. It is defined as an intermittent involuntary micturition during sleep in children over 5 years of age with at least two episodes per week and duration of more than 3 months [1]. Basically, NE is divided into non-monosymptomatic nocturnal enuresis (NMNE) and monosymptomatic nocturnal enuresis (MNE) according to whether there are daytime lower urinary tract symptoms. On the other hand, it is also classified into primary nocturnal enuresis (PNE) and secondary nocturnal enuresis (SNE) according to whether or not the duration of dry days is less than 6 months [1]. Secondary NE requires clinicians to identify and evaluate the diseases which NE is secondary to and treat them first. In PNE, NMNE usually means that children have more complex bladder dysfunction or other potential pathology and need to be referred to a specialist for further diagnosis and treatment. Although some children with MNE can be self-healing and the prevalence gradually decrease with age [2],

most treatments for NE cannot achieve high cure rates and may cause high relapse rates. This may result from the complexity and uncertainty of the etiology of NE and the use of inappropriate treatment.

2. Epidemiology

According to Jain et al.'s review, the prevalence of MNE varies from 3.8 to 18.9% in different countries [2]. The risk factors related to NE reported in different studies include constipation, positive family history, obstructive respiratory disorder, deep sleep, corporal punishment at school, urinary tract infection, etc. [3–6]. However, the effect of each factor on NE varies from study to study, and no universal conclusion is drawn. The results from different studies may be contradictory. For example, a few researches reported that the prevalence of NE was significantly higher in boys than the one in girls [3, 7], while other studies draw the opposite conclusion that girls' prevalence is higher [8]. The potential reasons for the contradiction of results in different studies performed in different countries may be related to the difference in diagnostic criteria followed by each survey, sample size, sampling method, questionnaire design, and cultural background in different regions. According to Wen's survey about NE in Chinese children, the overall prevalence was 4.07%, which is much lower than counterparts in other countries [9]. In it, Dr. Wen reported that Chinese parents would wake their children to void once they found children's dysphoria due to the fullness of the bladder. Besides, he also found that Chinese parents were more likely to withdraw the diaper for their children as early as possible, which is believed to be helpful for the children to build normal urination habits. Similar to the mechanism of alarm therapy, these actions may have a positive effect to promote the establishment of reflex between bladder filling feeling and urination. It is important to analyze epidemiological data, which may help us to understand the importance of the children and their parents' behavior and other complex physiological, pathological, and social psychological elements involved in the prevalence of NE.

3. Clinical diagnosis and treatment algorithm

There are a few diagnosis and treatment algorithms of NE proposed by the International Children's Continence Society (ICCS), the International Continence Society (ICS), and some other literatures with similarities and differences. In this part, the algorithm of the ICCS's practical consensus guideline is introduced and modified.

NE has many possible causes: genetic factors, renal physiological factors, deficiency of antidiuretic hormone (ADH, vasopressin) leading to nocturnal polyuria, bladder dysfunction, arousal disorder, maturation delay, circadian rhythm disorder, etc. Moreover, many associated diseases such as obstructive sleep-disordered breathing, constipation, fecal incontinence, attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD), obesity, psychological problems, etc. can also be seen in children with NE. These associated diseases should be identified in the clinical evaluation and be treated first. For children without those conditions, the increase in nocturnal urine production and nighttime bladder capacity reduction are the two main prototypes. To provide an outline in the diagnosis and management of NE, we build an algorithm after summarizing available guidelines. **Figure 1** is the clinical diagnosis and treatment algorithm adapted from the guideline of Walle et al [10]:

1. Clinical management tool is a medical history and symptoms collection form (see [10]).
2. Voiding diary (bladder diary) is not necessary.
3. After MNE is diagnosed, the 2012 guideline recommends directly the alarm and desmopressin treatment options. John Michael's review in 2014 recommends 6 weeks of urotherapy first and then evaluating the child to decide whether to take alarm or desmopressin [11].
4. EBC: expected bladder capacity, calculated as $\{30 + (\text{age in years} \times 30)\}$ in milliliters.
5. MVV: maximum voided volume, the largest urine volume of 24 h (see part bladder diary for details).



Figure 1.
Nocturnal enuresis algorithm (modified from Walle, 2012).

4. Treatment

4.1 Urotherapy

According to the 2006 ICCS's standardized terminology of lower urinary tract (LUT) function, urotherapy is defined as a nonsurgical and nonpharmacological treatment for LUT dysfunction [1]. It includes standard therapy which means the therapy is noninterventional and has specific interventions.

4.1.1 Standard therapy

The standard therapy usually has these components as below:

1. Health education. Health education refers to providing parents basic information about normal LUT function and the causes, risk factors, different treatments, and their implementation of MNE [1]. The clinicians should emphasize that the condition is common and can be healed by itself and that parents should have a positive attitude instead of thinking enuresis as a shame because this helps children to establish their motivation for active participation and reduce damage to their self-esteem, which is the key to treatment [12].
2. Lifestyle advice. Develop healthy drinking and eating habits: avoid foods or beverages that have a diuretic effect, such as theophylline or caffeine; eat early in the evening, with less oil and less salt; and no more water or food and fruit rich in fluid at least 2 h before going to bed. These all avoid excessive nighttime fluids in body which may lead to overmuch urine production during the night. However, for children with MNE, fluid restriction may have a risk of reducing bladder capacity resulting in a decrease in the ratio of bladder capacity to nocturnal urine output, and so nocturnal enuresis increases [13]. Therefore, adequate fluid intake during the day is important, especially during the morning and early afternoon hours [14]. It is also good for cultivating the child's feeling of bladder fullness. Moreover, a research indicates that holding exercises can increase the maximum voided volume of children with MNE, so it is better not to be active after dinner [15].
3. Developing regular voiding and bowel habits. As the ICCS recommended, children should develop a good habit of regular urination during the day and schedule to urinate before going to bed and in the early morning after waking up. The daily routine of micturition should be comprised of once in the morning, at least twice during school hours, and once each after school, at dinner, and before going to bed, with totally less than seven urinations during daytime [14]. Besides, parents should instruct the child to use a comfortable voiding posture to relax the pelvic floor muscles—and that means sitting on the toilet safely with the bottom and feet supported. Constipation is a common concomitant disease in children with NE, especially with NMNE. It is recommended to eat more foods rich in dietary fiber and develop regular bowel movements every day, best after breakfast. Based on current evidence, medication can be used to soften children's stools if necessary [14].
4. Voiding diary or bladder diary (VD or BD). According to the 2012 ICCS's practical consensus guidelines for MNE's management [10], BD is recommended to assess the children's voiding habit, especially for the families in which parents are unclear about children's voiding history. The most important function of BD is to evaluate the bladder capacity of children through daytime diary and

to assess the presence of nocturnal polyuria (NP) through nighttime diary. It is also helpful to distinguish NMNE through finding out daytime polyuria, stress urinary incontinence, urgency urinary incontinence, etc. A *daytime diary* should include at least fluid intake time, urination time, fluid intake volume, urination volume, and the occurrence of urinary incontinence and exclude the first urination after getting up in the morning. The recording time should be at least 3–4 consecutive days. Children attending school can choose to record two consecutive weekends [10]. In daytime diary, the most important thing that requires clinicians' attention is the largest urinated volume which can indicate the child's bladder capacity. It can be determined if the bladder capacity is reduced or increased when the maximum voided volume is <65% or >130% expected bladder capacity (EBC's calculation formula is shown in **Figure 1**). The *nighttime diary* should include at least urination time (if the child gets up to the toilet), urination volume, diaper weight overnight, first urination volume after getting up in the morning, dry night or not (there is any enuresis or not), and whether there is bowel movement that day. The recording time should be at least seven consecutive nights [10]. What the nighttime diary can tell the clinicians is the child's amount of urine produced at night by adding first urination after getting up in the morning, the nighttime diaper weight, and nocturnal urination volume to the toilet. If the total nighttime urine output exceeds 130% EBC, it is determined as nighttime polyuria (NP). Through analyzing individual BD, children with MNE can be classified into one of the four subtypes as shown in **Figure 1**. Then the corresponding treatment could be determined. In addition, by calculating a child's body surface area, we can find whether the 24-h urine volume >2 L/m², which means the child has polyuria; by observing a child's water taking, we can know if the child has polydipsia which is considered as a predictor of diabetes or kidney disease. It is worth noting that children with these conditions are not suitable to take desmopressin.

4.1.2 Specific interventions

Specific interventions comprise behavioral modification and nonbehavioral strategies including pelvic muscle floor training, biofeedback, electrical stimulation, etc. [1]. And the behavioral interventions can also be divided into simple and complex strategies based on whether it is a single action or they are composite interventions [16] (**Table 1**).

Simple behavioral Interventions	Reward systems
	Lifting or waking the children at night to urinate ¹
	Bladder training ²
	Fluid restriction
	Cleanliness training
Complex behavioral interventions	Dry bed training (DBT)
	Full-spectrum home training (FSHT)
	Arousal therapy

¹Lifting and waking therapy includes lifting with or without password and waking randomly or to a certain time.
²Bladder training includes retention control training, pelvic floor muscle training, sphincter control exercises, and stream interruption exercises.

Table 1.
Categories of behavioral interventions.

4.1.2.1 Simple behavioral interventions

Most of the simple behavioral interventions were initially presented in some early literatures, because the effects of first-line treatment on NE had not yet been determined at the time. They are often used in clinical treatment, but the efficacy is controversial since it lacks high-quality evidence. A systematic review about the efficacy and safety of simple behavioral interventions for NE has been published in the Cochrane Library. Unfortunately, only limited evidence is available. For most interventions only a single clinical trial was included, and therefore the data cannot be combined for meta-analysis except for the comparison between bladder training and alarm [16]. Furthermore, some other important limitations about the clinical trials were discussed in this review: for children with NE included in the trials, MNE and NMNE were not further distinguished; most trials had methodological deficiencies, and more than half of the trials reporting continuous outcomes did not report SDs; the trials' sample size was small, risk of bias was high, and the confidence interval was too wide; since there is a lack of long-term follow-up after the end of treatment, no data were available to assess the long-term efficacy of the interventions [16]. The following is a summary of this review's conclusion which needs to be cautiously referenced.

In the simple behavioral interventions referring to reward systems, lifting or waking the children, bladder training, and fluid restriction (*cleanliness training was not reviewed*), though all of them were more effective statistically than the control group, none of them had a better effect than others at the end of the treatment. When compared with alarm or different drugs, they were usually less effective except for bladder training which has no significant difference with drugs [16]. In terms of safety, adverse events were not reported in the included trials.

Bladder training is a behavioral therapy aiming to increase bladder capacity and strengthen the control of bladder in children. According to the review, bladder training seemed to be superior to the nonactive movements group in gaining less mean wet nights at the end of the treatment. However, there was no difference in the number of children who did not achieve 14 dry nights [16]. Another prospective trial further revealed that the basic bladder training's effects mostly were pronounced after the third month of treatment for the MNE children who did not receive any previous treatment. Therefore, for children who are not strongly willing to accept behavioral interventions, early administration of alarm or desmopressin is necessary [17]. But it seems to have good efficacy in children with NMNE [18].

Lifting without password is a controversial intervention because it allows the children to urinate while asleep, but it is useless to reduce the occurrence of nocturnal enuresis [19]. Being consistent with the conclusions of this review, a study also showed that the lifting without password group had a significantly higher proportion in the number of dry children than the control group and was even superior to lifting with password group and rewards group. In terms of long-term effect, both lifting groups had more dry children than the two other groups during 3 years follow-up [20].

4.1.2.2 Complex behavioral interventions

Dry bed training (DBT) is the oldest complex behavioral interventions with a multicomponent package of nighttime waking schedule, cleanliness training, reinforcement techniques, and other interventions. It has different versions and a few adapted versions with some components removed [21]. Full-spectrum home training (FSHT) is a combination with alarm, cleanliness training, and retention

control training in the daytime. To maximize the effect, the FSHT needs to be overlearned (giving extra fluids at bedtime after successfully becoming dry). Specific implementation steps of DBT and FSHT have been described by Brown and Glazener [22, 23]. In a Cochrane review of NE, complex behavioral interventions were compared with control, alarm, and other complex behavioral interventions. Moreover, complex behavioral interventions removing alarm were compared with control, alarm, and complex behavioral interventions supplemented by alarm. The conclusions were that DBT or FSHT was better than control in efficacy and relapse rate and marginally superior to alarm alone. Either complex behavioral interventions removing alarm or control intervention was inferior to alarm alone or complex behavioral interventions supplemented by alarm. There is no evidence for the comparison between complex behavioral interventions removing alarm and control. Additionally, adverse events were not described by the trials [23]. Unfortunately, the included studies in the systematic review have some limitations including small scale, small quantity, and poor quality. Besides, it has to be mentioned that the interventions are heavy burdens on families.

Alarm and reward system are the components of arousal therapy/training, which was reported to have a high efficacy and low relapse rate in an early literature [24]. However, they have not been recommended by the guideline [10] because there is not enough clinical evidence, which is similar to FSHT [25].

4.1.2.3 Nonbehavioral interventions

Biofeedback therapy and electrical stimulation therapy were originally used to treat voiding dysfunction, and now they have been tried to treat refractory MNE or PNE with a reported good efficacy. Dr. Hoekx and his colleagues prospectively evaluated the effect of bladder biofeedback in 21 boys and 3 girls (mean age 10.4 years). After treatment 17/24 patients showed good response that means they achieved totally dry. During the 60-month follow-up, 4 patients were lost, 15 were dry at night, and 4 continued bed-wetting. The proportion of children with small bladder capacity in responders is much less than the one in non-responders [26]. In a randomized clinical trial published in 2015, 54 children with PNE were included and randomly divided into interferential (IF) electrical stimulation group and control group. A responding rate was reported as 55.5 and 22% in the IF and control group at the 1-year follow-up ($P = 0.01$), respectively. In terms of the mean number of dry nights per week and the mean improvement score, the IF group was superior compared to control group. Additionally, no adverse events were reported [27]. In another trial, children with refractory MNE were randomly assigned to intra-anal biofeedback with behavioral therapy, electrical stimulation with behavioral therapy, and pelvic floor muscle training groups. The trial stated a total efficacy of three groups in the outcomes and that intra-anal ES group was superior to BF training group. But in these three outcomes, the method to assess nighttime bladder capacity with morning first urine volume is not accurate [28]. In short, there is no adequate clinical evidence to determine the therapeutic effectiveness of these NE treatments (Table 2).

Nonbehavioral interventions	Biofeedback (BF) ¹
	Electrical stimulation (ES)

¹Including bladder biofeedback and intra-anal biofeedback

Table 2.
Categories of nonbehavioral interventions.

4.2 Alarm

Alarm therapy, also known as enuretic alarm devices (EADs) or enuresis alarm treatment (EA), is a kind of therapy with sufficient evidence which shows a higher response rate and a superior long-time success than the control or other therapies. Although its relapse rate is still a little high, the addition of overlearning and dry bed training or avoiding penalties can reduce the rate by nearly half [29]. In terms of different types of alarms, there was no enough evidence to draw conclusions, neither did the comparison between alarm and other behavioral therapies [29]. Two other Cochrane reviews revealed that alarm had better effects than simple behavioral interventions, but not when compared with complex behavioral therapies [16, 23]. Some researchers believed the effect of alarm might be weakened if only the parents were waked by the alarm instead of the children. A result from Tsuji's study showed whether the parents or children themselves are waked by the alarm or the effectiveness of alarm is equal [30]. Apos E. et al.'s study published in 2018 stated excellent effects of alarm therapy for MNE, NMNE, PNE, and SNE children using alarm therapy and especially for NMNE children [31]. The ICCS guideline also recommended that the alarm should be considered as the therapeutic option for every child. Furthermore, those children who have motivated parents should be given a priority [14].

It has to be mentioned that alarm does not have an immediate effect. Normally, it often needs to take a period of time to achieve the expected efficacy. The appropriate course recommended by the ICCS is 2–3 months until children achieve 14 consecutive dry nights or the effect is not good [14]. Similarly, the ICS's recommendation is to evaluate the efficacy of alarm after at least 6–8 weeks [12]. It also states that the efficacy will increase with treatment duration; however, the ideal course of alarm has not been introduced [12]. In one study, a total of 455 children with PMNE were randomly divided into three groups and received 3, 4, and 5 months of uninterrupted alarm treatment, respectively. The results showed that children with 16–20 weeks' treatment had better curative effect [32]. Unfortunately, this study did not observe the effect with a longer follow-up. So we cannot conclude if the longer treatment can further increase the effect of alarm. In another study, NE children who were ineffective after 3 months' alarm treatment were randomized into two groups to receive a repeat alarm treatment for ≥ 3 months without interval and with an interval of more than 6 months, separately. The success rate in the latter group was significantly higher than the former, which means repeat alarm therapy with at least one interval may reawaken children's response [33]. Despite the small sample size, this study may provide new ideas for children who have no response to alarm treatment.

The possible mechanism of alarm therapy may be a gradual establishment of a conditioned reflex between bladder filling and waking. Evidence showed that it could increase the prepulse inhibition (PPI), similar to the effect of desamino-arginine vasopressin (dDAVP), which suggested that the alarm could also promote the maturation of the reflex control of NE [34]. In addition, a study reported that children's daytime functional bladder capacity increased markedly after treatment with alarm [35]. Therefore, the efficacy of alarm on children with NE may be achieved through multiple effects.

4.3 Desmopressin

Desmopressin is an arginine vasopressin analog that enhances the reabsorption of water by the distal convoluted tubules and collecting ducts of the kidney and inhibits the secretion of aldosterone. Schulz-Juergensen et al.'s study published in 2007 showed that 1-desamino-8-D-arginine vasopressin (dDAVP) could make

PMNE children's PPI upregulate to the age-related normal level. The authors offered a different explanation about dDAVP that it not only had a role in the kidney but also acted as a central neurotransmitter which has a positive effect on the delayed maturation of NE children's micturition reflex [36]. According to the results of this study, desmopressin has the ability to cure a substantial group of children with NE in theory. However, it is more complicated in practice with problems of how to choose the potential suitable children for desmopressin therapy. Moreover, what is the appropriate dose and course of treatment are also big issues. To assess the effect of desmopressin, a number of studies have been performed. Evidence showed that it could significantly reduce bed-wetting by 1–2 nights per week during the treatment, but there is no difference in wet nights per week compared with the placebo group. Additionally, when comparing with alarm therapy, lower effectiveness and higher subsequent relapse rate were reported in the desmopressin group according to a Cochrane review [37].

In general, children with nocturnal polyuria are suitable for desmopressin therapy. Basically, we can identify this subtype of MNE using the bladder diary. However, there is an evidence showing that children with NE may not present continuous nocturnal polyuria. Nocturnal urine production increases significantly on wet nights than the dry nights. Children without abnormal increase in nocturnal urine production do not respond to desmopressin [38]. This study revealed the polyuria characteristics for a subgroup of NE children and confirmed the efficacy of desmopressin for these children. Furthermore, some other studies also showed that desmopressin was not effective in children with low functional bladder capacity [39] and those with abnormal bladder volume and wall thickness (BVWT) [40], indicating that desmopressin's clinical use should carefully identify children with potential bladder dysfunction.

Referring to appropriate dose of desmopressin, there is an insufficient evidence to determine whether higher dose is more effective or not [37]. The recommended safe dose is 0.2–0.4 mg for tablets and 120–240 µg for melt formulation [14]. There is no enough evidence to state what is the appropriate course of treatment. Because of high relapse rate after treatment, it is advised to gradually reduce the drug dose instead of stopping it directly at the time of getting a complete response. For long-term safety, desmopressin is proven to be safe enough to use for several years. Water intoxication with hyponatremia is only a severe adverse event that needs to be concerned. Fluid restriction of 200 ml or less for the whole night is advised with desmopressin treatment [14]. Moreover, nasal spray reports more hyponatremia than oral formulations [41].

4.4 Pharmacotherapy (other than desmopressin)

Anticholinergic drugs are widely used for the management of NE since they can bind to choline receptors and produce antagonistic activity against acetylcholine and consequently relieve detrusor overactivity. They can be classified into M and N receptor blockers according to their selectivity for different receptors. M receptor blockers, also called as antimuscarinics, are more commonly used to treat NE. Generally, M receptors consist of five different subtypes, including M1, M2, M3, M4, and M5. Of those, M2 and M3 subtypes are mainly distributed in the bladder wall, and M3 has an upregulated expression in patients with overactive bladder. Therefore, the therapeutic mechanism of antimuscarinics is to inhibit the bladder M receptor, relax the detrusor, and consequently expand the bladder capacity. The mechanism determines that antimuscarinic drugs should be mainly used in treatment of NE children who are suffering from latent bladder smooth muscle spasm, detrusor overactivity, or decreased functional bladder capacity.

This kind of children usually has daytime symptoms of lower urinary tract and is classified as NMNE. However, some children diagnosed as MNE are also suitable for anticholinergic drug therapy because they have only nighttime detrusor overactivity or mild urinary tract symptoms during daytime. For children who do not respond to alarm or desmopressin therapy, anticholinergic agents are usually a kind of therapeutic option. The clinical application of anticholinergic drugs should focus on how to identify the children with indications through bladder diary and other diagnostic techniques. Studies to evaluate the efficacy of anticholinergic drugs and their combination with alarm or desmopressin on these children should be conducted as well.

Differing from anticholinergic drugs, the mechanism of tricyclic drugs in the treatment of NE is still unclear. The possible mechanism includes inhibiting rapid eye movement sleep to promote sleep arousal and stimulating antidiuretic hormone secretion. A Cochrane review showed that tricyclic drugs could reduce about one wet night per week, but most children relapsed after treatment which is similar to desmopressin and inferior to alarm [42]. In addition, most tricyclic drugs may cause serious side effects such as cardiotoxicity, so they are only used for the treatment of refractory or therapy-resistant NE. An exception is reboxetine. Neveus and his colleagues attempted to treat children with therapy-resistant NE using reboxetine, and they found that 59% of the patients reached a full response after 4 weeks of treatment. Moreover, during treatment, no significant cardiac toxicity was reported [43]. Lundmark et al. used reboxetine to treat therapy-resistant NE children and also achieved good results without significant cardiac adverse events [44]. Therefore, reboxetine may be a good therapeutic option instead of imipramine, but its effectiveness and safety need more clinical studies to prove.

4.5 Complementary and alternative approaches

Although a large amount of evidence has shown the effectiveness of conventional treatment including alarm and pharmacotherapy on NE [31, 45], these approaches cannot meet all the needs of the children and their parents. It is reported that as high as 30% of families discontinue the treatment of alarm on their own reason [46]. On the other hand, the side effects related to medications bother both children and their family members. Therefore, a number of parents are more likely to seek help from complementary and alternative medicine for their children. Being outside of conventional medicine, complementary and alternative medicine includes a series of medical approaches, such as acupuncture, herbal therapy, and massage. Recently, an increasing evidence has shown the efficacy of complementary and alternative medicine on management of NE.

4.5.1 Acupuncture

Acupuncture, as a component of traditional Chinese medicine, has been used to manage a number of chronic diseases. Even though acupuncture originates in China, its efficacy on various urological diseases has been recognized in industrial world [47]. A number of studies have demonstrated the effectiveness of acupuncture in treatment of NE. In a single-arm trial, Bjorkstrom et al. [48] showed that an 8-week treatment with 20 sessions of acupuncture decreased the episodes of NE and the sleep arousal threshold significantly in 65 and 50% of children, respectively, at the follow-up of 6 months. Another study further revealed that acupuncture might increase the nocturnal bladder capacity significantly in responders [49]. To assess the effect of acupuncture on NE, several systematic reviews were conducted. As presented in a part of Cochrane systematic review [50], Glazener et al. showed that acupuncture

might result in a more significant improvement for children with NE than sham intervention. Moreover, acupuncture seemed to have a lower failure rate than combination therapy with meclofenoxate, oryzanol, and thiamine. Six years later, the updated Cochrane systematic review [50] demonstrated the same result. Another systematic review showed that acupuncture in conjunction with other treatment could reduce the number of NE more significantly than other treatment alone [51]. It needs to be mentioned that some methodological limitations have to be taken into consideration when we analyze the evidence. These systematic reviews included the nonrandomized and quasi-randomized studies besides randomized controlled trials, which may weaken the level of evidence. To provide the high quality of evidence, a recent published systematic review excluded nonrandomized and quasi-randomized trials and showed that acupuncture might be more effective in management of NE than sham procedure or drug treatment [52]. However, some studies with the intervention of acupoint injection were included in the systematic review, which may make the results controversial. As is known, acupuncture only provides physical effect, while both physical and chemical effects are involved in acupoint injection.

To further provide evidence, we designed and conducted a systematic review. After performing a comprehensive search of medical literature, including Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CBM, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform, on February 22, 2019, a total of 238 randomized controlled trials were reviewed, and 10 of them with 953 randomized participants (441 in acupuncture group and 412 in control group) were included. We found that compared with the other treatment, acupuncture resulted in significantly higher complete response rate [OR = 2.41, 95%CI (1.41, 4.93) $P = 0.002$], so did the significance when compared with conventional drug, sham procedure, and herbal therapy, respectively. Moreover, although acupuncture did not reduce the average number of NE in comparison with other treatment, a significant decrease was found when compared to the sham intervention [MD = -1.49, 95%CI (-2.26, -0.72) $P = 0.0002$]. In terms of adverse events, there was no significant difference between acupuncture and other treatment [OR = 0.62, 95%CI (0.04, 8.72) $P = 0.72$]. Based on our results, acupuncture may have a better effect in management of NE, when compared to conventional drug, sham procedure, and herbal therapy, respectively.

The potential mechanism of acupuncture's effectiveness in managing NE might be the regulation on bladder function and secretion of antidiuretic hormone. A study assessed the effect of acupuncture on urodynamic parameters in children with NE and found acupuncture could suppress the detrusor overactivity [53]. On the other hand, an animal experiment showed that acupuncture could downregulate the concentration of arginine vasopressin in the hypothalamic paraventricular nucleus and upregulate the concentration of arginine vasopressin in the hypothalamic supraoptic nucleus, periaqueductal gray, caudate nucleus, and nucleus raphe magnus [54], which may cause an antidiuretic effect.

4.5.2 Herbal therapy

Herbal therapy is an important component of traditional medicine. About 3500 years ago, Papyrus Ebers described that cypress, juniper berries, and beer might be used to treat NE, which is the earliest record for the treatment of NE. Although there is lack of enough evidence, some herbs, such as St John's wort (*Hypericum perforatum*), infusions of horsetail, or corn silk (*Zea mays*), are considered to be helpful to regulate bladder function [55]. Hosein et al. performed a double-blind randomized controlled trial to evaluate the effectiveness of chamomile oil in treating NE, in which 80 patients were allocated to receive chamomile

oil or placebo. After 2 weeks treatment, the patients' mean wet night frequency in chamomile oil group decreased from 8.2 to 5.6 nights/2 weeks, while no significant difference was found in placebo group [56]. We hope more clinical trials can provide more evidence for the efficacy of herbal therapy in future.

4.5.3 Massage and chiropractic

Both massage and chiropractic are a kind of manipulative therapy acting on the body with appropriate pressure. The former focuses on the relaxation of muscle, while the latter centers on the regulation of spinal articulations. They can be the therapeutic options for NE since their effectiveness has been reported. An early study attempted to treat five children with NE using massage which pressed the acupoint located in the creases between the first and the second and the third phalanx of the 5th finger. After an average of 20 sessions of therapy, two children achieved complete recovery, and one got partial recovery [57]. In another study, Yuksek et al. performed an efficacy comparison of massage with oxybutynin. After 6 months treatment, 83.3% of patients in massage group experienced a significant improvement, which is better than 58.3% in oxybutynin group [58].

In a case series study, 171 children with NE were treated by chiropractic. After 2 weeks treatment, the median episodes of NE decreased from 7.0 per week at baseline to 5.6 per week and further dropped to 4.0 per week at the end of treatment [59]. Another finding of the study is that the more severe symptoms children had, the less benefit they got from the treatment, which means those with mild to moderate NE might be suitable for chiropractic. Reed et al. designed and conducted a 10-week controlled clinical trial, in which children with NE received chiropractic or sham intervention. After the treatment, a significant reduction was observed in children's mean wet night frequency (from 9.1 to 6.7 nights/2 weeks) in chiropractic group. By contrast, the counterpart in sham intervention group did not change markedly (12.1 vs 12.2 nights/2 weeks) [60]. Van Poecke and his colleague found that the resolution rate within 1 year in children who received chiropractic was about 66.6% after analyzing the data of 33 patient records [61].

5. New about diagnostic and treatment

Enuretic bladder capacity is a big issue discussed in some recent research. Researchers are more likely to use the reduction in maximum voiding volume (MVV) on bladder diary to determine the decreased nocturnal bladder capacity (NBC). However, it might be unreasonable because a study found the enuretic bladder capacity of enuresis children was significantly less than their daytime functional bladder capacity (FBC), while healthy children's NBC was the same as FBC [62]. Kim et al.'s study also showed that the proportion of NE children with small NBC and small MVV was quite different. The accuracy using decreased MVV to identify small NBC is only medium to low [63]. Another study performed by Borg et al. measured the difference in diaper weight between the early part and the later part of the night, as the enuretic bladder capacity, in MNE children with normal MVV, and found that 82% of children had less bladder capacity than MVV during enuresis, even less than 65% of expected bladder capacity [64]. These studies indicate that although small MVV can be used to determine the reduction of FBC, it cannot assess accurately NBC or enuretic bladder capacity. If pediatricians manage MNE children with normal MVV with desmopressin following the ICCS guidelines, these children may still experience nocturnal

enuresis due to a mismatch between bladder capacity and urine volume at night. Therefore, a new method for assessing NBC and enuretic bladder capacity needs to be explored.

Barroso et al. assessed the efficacy of a new device, which is the combination of alarm and electrical stimulation to the pelvic floor muscles, for NE. This device presented an advantage that helps children to achieve no wet beds during the period of treatment. On the one hand, pelvic floor muscle contraction induced by electrical stimulus may cause an increased urethral closure pressure, which allows children to keep dry during nighttime. On the other hand, alarm would also be triggered by the humidity sensor, and children would be waked to void [65]. This device needs more trials to determine its effectiveness and safety. Additionally, there was an intelligent autonomous alarm using ultrasound and smartphone ML techniques raised in 2019. It could monitor the bladder and trigger before the voiding desire. It also has the advantage to achieve totally dry bed during treatment [66].

6. Conclusions

Standard therapy should be applied to every child when he first visits the clinic. Then clinicians follow the diagnosis algorithm to distinguish MNE from NMNE and determine which subtype the child is. According to the ICCS's guideline [10], MNE children with normal nocturnal urine volume (normal or reduced MVV) should choose the alarm therapy. It is believed as the most effective single-therapy with the lower recurrence rate and has efficacy for most types of MNE, even NMNE. The addition of overlearning can reduce the relapse rate of alarm. Therefore, it is necessary to perform overlearning after the success of the alarm treatment. Complex behavioral therapies supplemented by alarm are more effective than alarm and can reduce the recurrence rate. It can be advised to families with better motivation and seeking for better efficacy. Desmopressin should be used for the treatment of MNE children with polyuria (normal or reduced MVV). To avoid relapse, the drug can be taken for a long time and then gradually reduced.

The guideline recommended small MVV and NP children to use combination therapy of alarm and desmopressin [10]. The addition of alarm can increase the long-term efficacy of desmopressin [37]. However, combination therapy seems not to reduce the number of children who do not achieve 14 consecutive dry nights compared with alarm alone [29], indicating that patients who do not have full response to these two therapies may be mostly overlapped.

For refractory NE, clinicians should reassess children's potential physiological malformations and neurogenic bladder diseases using MRI, urodynamics, cystoscopy, urography, etc. if necessary. After first-line treatment failure, children with detrusor overactivity or decreasing functional bladder capacity can choose anticholinergic drugs. Other children can choose tricyclic drugs, biofeedback therapy, electrical stimulation interventions, acupuncture, massage and so on, or a combination of first-line therapy and second-line therapy.

In summary, after meticulous diagnosis and assessment and appropriate treatment with sufficient evidence, most MNE children can get a great relief or even cure.

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