FUNCTIONAL UROLOGY

Traditional and innovative interventions in the management of enuresis

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Introduction Enuresis (NE) is a socially stigmatising and stressful condition affecting children's and parent's quality of life. The aim of this review was to evaluate and summarize the current knowledge about the pharmacological and non-pharmacological traditional and innovative treatments in children with NE.
Material and methods We examined the following bibliographic electronic databases: PubMed and the Cochrane Library, from January 2000 until July 2023. The search was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (8) and was limited to English-language papers that focused on enuresis in patients under 18 years old. Each paper that met the eligibility criteria was reviewed and analyzed in full text by three authors and any discrepancies among them were solved by debate. Due to the heterogeneity of the articles examined, we focused on a qualitative analysis.
Results Overall, we identified 560 records through database searching. As first step, we excluded 46 articles in non-English language, 6 records whose related articles were not available, 8 articles concerning ongoing trials and 210 duplicated papers. As second step, we eliminated 215 records by evaluating only title and abstract because they did not match the inclusive criteria we mentioned before. Of the remaining 75 studies, we excluded 34 through a further discussion among authors upon the reliability of data. Thus, 41 selected articles were included in the review.
Conclusions Multiple treatment approaches, both pharmacological and non pharmacological, have been established and validated to reduce signs and symptoms of NE and improve quality of life and the social and emotional discomfort experienced by children. The aim of pediatrician is to identify the right therapy protocol for very single child, evaluating the best approach for him and the family.

Key Words: enuresis ‹› management ‹› treatments

INTRODUCTION

Enuresis (NE) is a socially stigmatising and stressful condition affecting children's and parents' quality of life. According to the International Children's Continence Society (ICCS), NE is defined as a nonvoluntary intermittent bedwetting while sleeping in children, especially aged 5 years or more, and more frequent in males (the male:female ratio is 3:1) [1].

The prevalence of NE is variable: it is above 10% among 6-year-olds, around 5% among 10-year-olds, and 0.5–1% among teenagers and young adults [2, 3]. NE is subdivided into primary and secondary variants. Primary NE, the most common type, occurs when the child has never experienced a period of nighttime dryness lasting longer than 6 months, while secondary NE occurs when nonvoluntary discharge of urine returns after at least a 6-month pe-

riod of nighttime dryness. The underlying causes of these 2 conditions are different: primary NE is the result of the simultaneous presence of several factors such as the failure to arouse from sleep despite receiving stimuli combined with either excessive urine production, small capacity of the bladder, or the detrusor overactivity. The increased arousal thresholds do not, however, mean that these children sleep well; in fact, sleep quality among enuretic children is often poor [4, 5]. There is also a genetic predisposition to primary NE, probably involving chromosomes 12, 13, and 21; this is confirmed by the increased incidence of this disease in children whose parents suffered from it. The incidence is about 15% in children whose parents did not experience NE, 44% in children with only one parent who suffered from it, and 77% if both parents experienced NE [6]. Secondary NE is caused by either the new onset of a medical condition, such as urinary infection, hypothyroidism, renal disease, obstructive sleep apnoea, diabetes insipidus, diabetes mellitus, or by a new psychological stress. Another important clinical classification divided NE into monosymptomatic (MNE) and non-monosymptomatic enuresis (NMNE): the latter term is reserved for those children who, in addition to their bedwetting, have daytime lower urinary tract symptoms (LUTS) such as urgency, daytime incontinence, voiding difficulties, and altered daytime voiding frequency. Many pharmacological and non-pharmacological approaches have been proposed in the management of NE, the treatment of which depends on coexisting disorders, the subtype of enuresis (MNE or NMNE), the severity of the problem, the child's motivation, and the compliance of their parents [7]. While the treatment of secondary NE coincides with the treatment of the underlying medical condition that causes it, the first-line treatments for primary NE are drugs (especially desmopressin in MNE and anticholinergics in NMNE) and behavioural protocols. The aim of this review was to evaluate and summarize the current knowledge about the pharmacological and non-pharmacological traditional and innovative treatments in children with NE.

MATERIAL AND METHODS

We examined the PubMed and the Cochrane Library bibliographic electronic databases from January 2000 until July 2023. The search was guided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [8] and was limited to English-language papers that focused on enuresis in patients under 18 years old. To be considered eligible for the review, papers had to include the following components: 1. subjects (children) with diagnosis

of enuresis; 2. who received pharmacological and non-pharmacological approaches as treatment; 3. clinical outcomes evaluated in short- and long-term period. We excluded: non-English-language papers and studies in which clinical outcomes were not evaluated or were not statistically significant. The key words used for the search across electronic databases were as follows: 'enuresis' or 'nocturnal enuresis' or 'bed-wetting' and 'pharmacological treatment' or 'drugs' or 'desmopressin' or 'oxybutynin' or 'anticholinergics' or 'imipramine' or 'mirabegron' or 'non-pharmacological treatment' or 'alarm' or 'dietary' or 'pelvic floor training' or 'bladder advice' or 'hypnosis' or 'acupuncture' or 'comorbidity'. The abstracts of the papers were assessed by a single reviewer (PF), who strictly applied the inclusion/exclusion criteria mentioned above to decide whether a paper was eligible for full review. Each paper that met the eligibility criteria was reviewed and analysed in full text by 3 authors (PF, IC, and MZ), and any discrepancies between them were solved by debate. Due to the heterogeneity of the articles examined, we focused on a qualitative analysis (Figure 1).

Data extraction and ethics statements

The data extracted from each eligible paper included the following: study design, study population characteristics, type of treatment, and clinical outcomes. In this review, we analysed the current literature on the main pharmacological and non-pharmacological treatment in children with enuresis. Thus, ethical approval was not required.

RESULTS

Overall, we identified 560 records through database searching. As a first step, we excluded 46 articles in non-English language, 6 records whose related articles were not available, 8 articles concerning ongoing trials and 210 duplicated papers. As a second step, we eliminated 215 records by evaluating only title and abstract because they did not match the inclusive criteria we mentioned before. Of the remaining 75 studies, we excluded 34 through a further discussion among the authors upon the reliability of data. Thus, 41 selected articles were included in the review. The detailed selection of the literature is shown in Figure 1. The characteristics of all included studies are summarised in Table 1 and Table 2.

Pharmacological treatment

Many pharmacological treatments have been studied for NE, and both desmopressin and anticholinergics
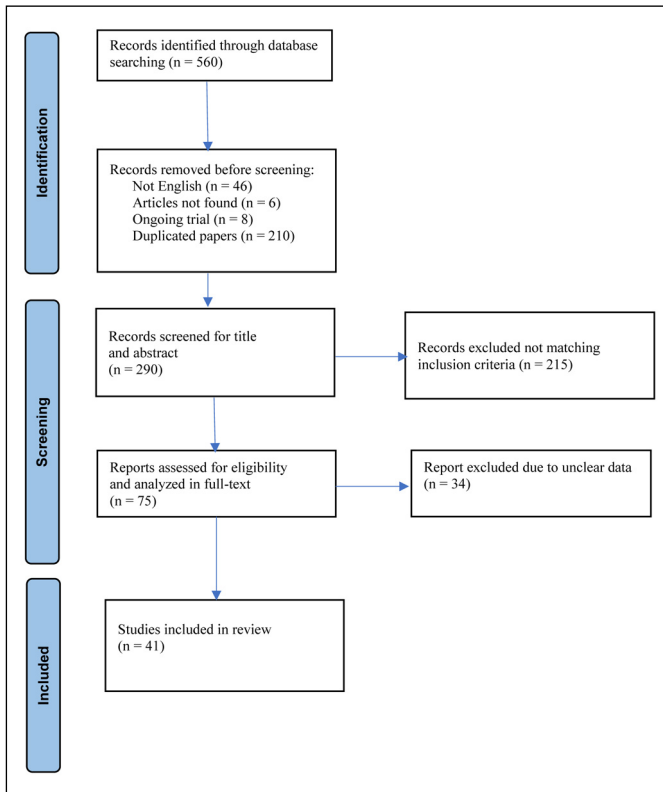
Figure 1. *The detailed summary of the literature search.*

are the main drugs used nowadays by paediatricians as a first-line approach.

Desmopressin (dDAVP) is considered the first-line treatment for children who do not respond to behavioural interventions alone or for those who need an immediate response (for example in the case of sleeping away from home) [1]. It is an analogue of the antidiuretic human hormone vasopressin (or antidiuretic hormone): it acts by increasing the reabsorption of fluid from the renal tubules and decreasing urine production. About 80% of children subjected to dDAVP have a good response rate but with a high incidence of recurrence at the end of the therapy. For example, Kwak et al. in a randomized controlled trial showed that 77.8% of the desmopressin group achieved a successful result, but about 50% experienced a relapse when treatment stopped [9]. Van Herzeele et al. and Kruse et al. evaluated possible predictive factors to desmopressin response, and they demonstrated that desmopressin response rates were higher in children with greater age, while Dehoorne et al. showed that nocturnal polyuria as an isolated factor cannot dependably predict a desmopressin response, even if the functional bladder capacity is also considered [10, 11, 12]. Bladder structural and functional features have been evaluated in children subjected to desmopressin therapy.

Hamano et al. found that desmopressin was less effective in children with a low functional bladder capacity, and Montaldo et al. suggested the use of anticholinergic agents for a subset of children with enuresis, who had a restricted bladder capacity and thickened bladder wall [13, 14]. Hara et al. conducted a molecular investigation documenting urinary aquaporin 2 as a biomarker of the effectiveness of desmopressin treatment during therapy, and plasma copeptin levels before treatment as a predictor factor of desmopressin response [15]. Desmopressin must be taken 1 hour before going to sleep and its intake should be implemented with a reduction in fluid intake for the following 8 hours [16]. It is available in oral tablets, in doses of 0.2–0.4 mg, and oral quick-melting lyophilizate (MELT), available in doses 60–120–240 μg. Two therapy protocols have been proposed: starting with the full dose and titrating down after a week/in the case of good treatment effect or starting with the lower dose and increasing until the response dose. In either case, the efficacy is usually immediately evident and there is no recommendation for prolonged medication for more than 2 weeks in a child who shows no beneficial effects [17]. Even if the safety of both formulations has been assessed, it seems that the clinical efficacy and pharmacological properties of the MELT formulation are superior to those of tablets. Juul et al. and Schulz-Jurgensen et al. found that desmopressin MELT, compared with the tablet, improved the probability of being a responder, and that switching from tablet to MELT formulation increased patient compliance, which was associated with increased efficacy [18, 19]. Moreover, while there is consensus that therapy with dDAVP tablets should be discontinued in a structured withdrawal program, Ferrara et al. demonstrated that a structured withdrawal program from MELT therapy does not offer advantages compared to an abrupt termination [20, 21]. Vande Walle et al. conducted a clinical trial to determine the pharmacodynamic properties of oral lyophilizate formulation of desmopressin and to identify the dosages that could provide a duration of action corresponding to a typical length of night-time sleep in children with NE. They found that a small dose range (120–240 μg) is likely to control diuresis for a period corresponding to a night's sleep in most children even if some patients required a higher dose to obtain antidiuresis for the complete night [22]. Lottmann et al. in an open-label, randomised, cross-over study evaluated the preference of children and adolescents with NE for vs. tablet treatment. They registered a high preference for MELT formulation with similar levels of efficacy and safety at lower doses than those of the tablet [23]. Desmopressin can be

Table 1. *Pharmacological treatments*

Study	Study design	Sample size	Mean Age (years)	Sex prevalence	Type of treatment	Main outcomes
Kwak et al. (2010)	Randomized controlled trial	104 children with MNE	8.1 (desmopressin group) 8.6 (enuresis alarm group)	Group desmopressin 45 boys 9 girls Group enuresis alarm 34 boys 16 girls	54 desmopressin 50 enuresis alarm	Successful result in 77.8% of the desmopressin group and 82% of the enuresis alarm group Full response in 37% and 50% of the two groups Relapse in 50% of the desmopressin group and 12% of the enuresis alarm group
Kruse et al. (2001)	Clinical trial	399 children with primary NE	Not mentioned	295 boys 104 girls	Desmopressin	134 of the responders (71%) needed 40 mg desmopressin 29 (59%) of the full responders needed 20 mg
Dehoorne et al. (2007)	Clinical trial	125 children with MNE subdivided into 2 Groups (63 full responders and 62 nonfull responders)	Full responders: 9.9 Nonfull responders: 8.7	Full responders: 45 boys 18 girls Nonfull responders: 39 boys 23 girls	Desmopressin	No differences in pretreatment values of functional bladder capacity, circadian rhythm of urine production or urine osmolality were found between desmopressin full responders and nonfull responders.
Hamano et al. (2000)	Clinical trial	114 children with MNE	9.3	88 boys 26 girls	Desmopressin and retention control training (RCT)	Improvement of 38.9% of desmopressin children vs 23.3% of RCT children In the DDAVP group, the functional bladder capacities at baseline in responders and nonresponders were 82 ±22% and 56 ±20% of the predicted bladder capacity
Montaldo et al. (2012)	Randomized controlled trial	206 children with MNE	10.6 ±2.9	117 boys 89 girls	Desmopressin plus oxybutynin	No difference between the 120 µg and 240 µg patients Higher rate of full and partial responses (45% success) in the desmopressin plus oxybutinin group Lower bladder volume and wall thickness index in responders to desmopressin plus oxybutinin
Hara et al. (2017)	Clinical trial	32 children with NE and polyuria	8.1	23 boys 9 girls	Desmopressin	After 8 weeks of treatment significant correlation between day/night ratio of aquaporin 2 and percentage of wet nights. In responders there was a significant difference in the change in aquaporin 2 day/night ratio from before treatment to complete remission For plasma copeptin the baseline day/night ratio for responders at 120 µg was significantly lower than in the 240 µg nonresponder group
Juul et al. (2013)	Randomized controlled trial	221 children with NE	9.6 ±2.4	158 boys 63 girls	Desmopressin	Greater probability of having an amelioration for desmopressin melt compared with desmopressin tablet (OR = 2; 95 % CI, 1.07–3.73). The dose of desmopressin also significantly increased the probability of amelioration, with an OR of 3.05 favouring the lower dose melt 120 µg/tablet (0.2 mg) compared with the higher dose melt 240 µg/tablet (0.4 mg)
Schulz-Jürgensen et al. (2016)	Randomized controlled trial	134 children with NE	Not mentioned	Not mentioned	Desmopressin	Less difficulties in taking the medication and forgotten doses, higher treatent satisfaction and greater reduction in wet nights with the melt than with the tablet formulation
Ferrara et al. (2014)	Randomized controlled trial	81 children	8.64	Not mentioned	Desmopressin	47/81 (58.02%) responded to therapy 24/47 (51.06%) were randomly assigned to withdraw suddenly and 23/47 (48.94%) to withdraw gradually. One month after the end of treatment, relapse occurred in 11/23 (47.83%) of the structured withdrawal program group and in 11/24 (45.83%) of the abrupt termination group

Table 1. *Continued*

Study	Study design	Sample size	Mean Age (years)	Sex prevalence	Type of treatment	Main outcomes
Vande Walle et al. (2006)	Randomized controlled trial	72 children with primary NE	Not mentioned	Not mentioned	Desmopressin	Mean duration of action of desmopressin at the lowest osmolality threshold level was 3.6–10.6 h, according to dose; for the highest threshold, the values were 1.3–8.6 h.
Lottmann et al. (2007)	Randomized controlled trial	221 children with NE	9.6 ±2.4	156 boys 65 girls	Desmopressin	56% preferred the MELT formulation Efficacy similar for both formulations (MELT: 1.88 ±1.94 bedwetting episodes/week; tablet: 1.90 ±1.85 episodes/week) Compliance was 94.5% for MELT patients vs. 88.9% for the tablet
Ravanshad et al. (2019)	Randomized controlled trial	40 children with NE	Not mentioned	Not mentioned	Desmopressin plus imipramine	Better recovery in 18 of 20 patients treated with combination therapy after 1 month with higher frequency of recovery (83.3%)
Kim et al. (2021)	Observational study	103 children with idiopathic overactive bladder	Not mentioned	Not mentioned	Mirabegron and solifenacin	The age-adjusted bladder capacity ratio increased from 0.71 to 0.96 (p <0.001) and from 0.57 to 0.97 (p = 0.002) after solifenacin and mirabegron use, respectively. Decreased bladder capacity before medication was associated with responding to medication (odds ratio, 7.41; p = 0.044)
Esteghamati et al. (2023)	Randomized controlled trial	40 children with MNE and NMNE desmopressin-resistant	Not mentioned	Not mentioned	Desmopressin plus tolterodine Desmopressin plus indomethacin	Mean (SD) percent in NE reduction was: 1 month 58.86 (7.27)% vs 31.18 (3.85)% 3 months 69.78 (5.99) % vs 38.56 (3.31)% 5 months 84.84(6.21) % vs 39.14 (3.63) %; At 5 months, complete response to treatment was only observed with D+T, while treatment failure was significantly higher with D+I (50% vs 20%)
Kamperis et al. (2016)	Randomized controlled trial	23 children with MNE, nocturnal polyuria, and partial or no response to desmopressin	9.1 ±2.3	19 boys 4 girls	Desmopressin plus indomethacin	The addition of indomethacin to desmopressin significantly reduced nocturnal urine output (from 324 ±14 ml to 258 ±13 ml, p <0.001). This did not lead to more dry nights in all children, and we found no statistically significant reduction in enuresis frequency (from 68% ±0.1 to 56% ±0.1, p = 0.24).
Ghanavati et al. (2021)	Randomized controlled trial	62 children with NE	8.70	Not mentioned	Solifenacin plus desmopressin Tolterodine plus desmopressin Desmopressin	Desmopressin plus solifenacin 19 of 20 patients (95%) achieved complete remission Desmopressin 14 of 22 patients (63.63%) achieved complete remission Desmopressin plus tolterodine 17 of 20 patients (85%) had complete remission
Austin et al. (2008)	Randomized controlled trial	34 children with NE refractory to the maximal dosage of desmopressin	10.50	24 boys 10 girls	Desmopressin plus anticholinergic medication	Long-acting tolterodine group had a higher rate of full and partial responses (44% success), compared with the placebo group (31% success). Larger proportion of patients who exhibited a complete lack of response (0% change) in the placebo group (44%), compared with the longacting tolterodine group (16.5%)
Lee et al. (2005)	Clinical trial	145 children with NE	7.8	100 boys 45 girls	Desmopressin Imipramine Desmopressin plus oxybutynin	Frequency of nocturnal enuresis before and after 6 months of treatment Combination therapy from 13.3 ±3.4 to 3.7 ±5.4 Desmopressin from 12.0 ±3.5 to 4.0 ±4.6 Imipramine from 13.2 ±2.9 to 9.3 ±8.3

Table 2. *Non-pharmacological treatments*

Study	Study design	Sample size	Mean Age (years)	Sex prevalence	Type of treatment	Main outcomes
Van Leerdam et al. (2004)	Clinical trial	37 children (group 1) with NMNE	7.7 (group 1)	Group I 25 boys 12 girls	Alarm treatment	Group I: 65% became dry at night and 38% became dry during the day
		37 children (group 2) with MNE	7.8 (group 2)	Group II 21 boys 16 girls		Group II: 75% became dry
Ozgür. et al. (2009)	Clinical trial	40 children with MNE	8.1	Not mentioned	Alarm treatment	Positive outcome in 27 patients with a full response in long-term follow-up (response rate 32.5%)
Taneli et al. (2004)	Clinical trial	28 children with MNE	Not mentioned	Not mentioned	Alarm treatment	The pre- and post-treatment maximum functional bladder capacity was 178.35 ±87.86 ml and 243.03 ±102.84 ml, respectively and the pre- and post-treatment mean day-time bladder capacity was 111.11 ±45.87 and 148.445 ±7.68 ml. The maximum nocturnal bladder capacity was found to be increased from 177.85 ±84.95 to 255.25 ±124.52 ml
Butler et al. (2007)	Clinical trial	12 children with NE	8.75	6 boys 6 girls	Alarm treatment	4 children (AVP responders) became dry, with concomitant increases in both mean corrected AVP (12.2 pg/min/Cosm pre-treatment vs 45.5 pg/min/Cosm post-treatment) and mean osmolality (480 mmol/kg pre-treatment vs 800 mmol/kg post-treatment). 4 children (AVP non-responders) showed an evident increase in mean osmolality (690 mmol/kg pre-treatment vs 890 mmol/kg post-treatment)
Kirill V Kosilov et al. (2018)	Randomized controlled trial	455 children with MNE	11.4	294 boys 161 girls	Alarm treatment Group A (n = 139) 12 weeks Group B (n = 136) 16 weeks Group C (n = 139) 20 weeks.	Success rate higher in groups B (80.7%) and C (85.5%) than in group A (67.4%) with no statistically significant difference between groups B and C
Tsuji et al. (2018)	Clinical trial	78 children with MNE	9.2	48 boys 30 girls	Alarm treatment in family assisted group (44) and alarm control group (34)	Full response and partial response in 36.4% and 20.5% in the family assisted group, and 26.5% and 29.4% in the alarm control group
Naitoh et al. (2005)	Clinical trial	105 children with MNE	9.4	76 boys 29 girls	37 alarm monotherapy 35 desmopressin with an alarm 33 imipramine with an alarm	Improvement rate of 80% in the desmopressin group and 79% in the imipramine group and 59% rate in the monotherapy group. No relapse in the monotherapy group
Ferrara et al. (2015)	Clinical study	137 children with MNE	Not mentio-ned	102 boys 35 girls	67 desmopressin and dietary advices (group A) 70 only desmopressin (group B)	Higher response rate and a lower number of relapse in group A vs group B with 67.2% of responders in group A vs 58.6% in group B, after 3 months of therapy and 31.1% of relapse in group A vs 46.3% in group B one month after the end of treatment
Campos et al. (2019)	Randomized controlled trial	38 children with NE	Group I 9.5 Group II 7 Group III 8	17 boys 21 girls	Group I standard urotherapy Group II standard urotherapy associated with pelvic floor training Group III standard urotherapy associated with pelvic floor training and oxybutynin	Complete success after 12 weeks: Group I: 58% Group II: 73% Group III: 55% Complete success after 2 years: Group I: 63% Group II: 75% Group III: 60%

Table 2. *Continued*

Study	Study design	Sample size	Mean Age (years)	Sex prevalence	Type of treatment	Main outcomes
Vesna et al. (2011)	Randomized Controlled Trial	86 children with NE	7.1	Not mentioned	Group A diaphragmatic breathing exercises and pelvic floor retraining in addition to standard urotherapy Group B only standard urotherapy.	Urinary incontinence and nocturnal enuresis were cured in a significantly larger number of children in group A than in group B. Bell shaped uroflowmetry curve was observed in 36 patients in group A and only 4 children in group B.
Van Kampen et al. (2009)	Randomized Controlled Trial	63 children with NE	Not mentioned	Not mentioned	Experimental group (32) full spectrum therapy with pelvic floor muscle training Control group (31) Full spectrum therapy without training	No significant difference in treatment outcome, duration, maximal voided volume and relapse between the 2 groups. 89% became dry within 6 months. During the year after treatment 33.3% and 37.9% of the experimental and control groups relapsed, while the relapse rate at 1 year was 7.4% and 20.7%, respectively.
Garcia-Fernandez et al. (2020)	Randomized Controlled Trial	48 children with NE	7.6 ±2.5	14 boys 34 girls	Squatting exercises	41/48 children were cured of both daytime/night-time enuresis. A total of 32 (68%) children with constipation 92% cured; 9 (19%) soiling (all cured).
Zivkovic et al. (2012)	Randomized controlled trial	43 children with NE and urinary incontinence	7.5	15 boys 28 girls	Standard urotherapy plus diaphragmatic breathing and pelvic floor exercises	After one year of therapy, urinary incontinence was cured in 20/24 (83%), nocturnal enuresis in 12/19 children (63%), while 13/19 children (68%) were UTI free. Bell-shaped curve was observed in 36/43 children
Tkaczyk et al. (2017)	Prospective interventional multicenter trial	49 children with MNE	7.2	36 boys 13 girls	Basic bladder advice	Mean number of wet nights decreased after 3 months from 8.9 to 5.9 episodes every 2 weeks. BBA was fully successful in 2% o the children after 30 day, 12% after 60 days, and 18% after 90 days
Eliezer et al. (2021)	Clinical study	39 children with MNE and NMNE plus behavioural disorders	10.3 ± 2.0	27 boys 12 girls	Standard urotherapy Combination therapy with specific urotherapy or pharmacotherapy.	Following 3-month review, 14 (38%) children continued to receive standard urotherapy, while 15 (41%) children were transitioned to combination therapy. At 6-month review, complete/partial response was seen in 62% (23/37) and no response in 16% (6/37); with 32% (12/37) responding to standard urotherapy alone.
Borgström et al. (2022)	Randomized controlled trial	60 children with NE	7.2	44 boys 16 girls	Group A BBA Group B enuresis alarm Group C no treatment	The median number of wet nights out of 14 before and at the end of treatment were in group A (n = 20) 12.5 and 11.5, in group B (n = 22) 11.0 and 3.5 and in group C (n = 18) 12.5 and 12.0. The difference in reduction of enuresis frequency between the groups was highly significant (p = 0.002), but no difference was found between basic bladder advice and controls.
Cederblad et al. (2015)	Randomized controlled trial	40 children with NE	6 y	29 boys 11 girls	Group A BBA for 1 month and then alarm therapy Group B alarm therapy	No reduction of NE frequency in group A. 4 children in group A had a partial or full response to bladder training, and 2 of these children relapsed during alarm therapy.
Hascicek et al. (2019)	Randomized controlled trial	63 children with MNE	Group I 9.5 Group II 8.5 Group III 9	40 boys 23 girls	Group I behavioural therapy Group II behavioural therapy with a written checklist for parents Group III desmopressin treatment plus verbal behavioural therapy	High rates of treatment compliance in Gropu II. The treatment response rates in Group I were significantly lower compared to those of Group II and III with no statistical difference determined between Groups II and III

Table 2. *Continued*

Study	Study design	Sample size	Mean Age (years)	Sex prevalence	Type of treatment	Main outcomes
Kajbafzadeh et al. (2015)	Randomized controlled trial	54 with primary NE	8.7 ±2.5	31 boys 23 girls	Control group standard urotherapy only Interferential (IF) electrical stimulation group standard urotherapy + IF electrical stimulation	15/27 (55.5%) and 6/27 (22%) of children in the IF and control groups responded to treatment at the 1-year follow-up. The mean number of wet nights per week in the control and IF groups decreased from 5.4 ±2 and 5.7 ±2 to 3.3 ±3 and 1.1 ±2, respectively, at first evaluation. The mean improvement score in the IF group was significantly higher than that of the control group after 1 year (78 vs 46%).
Mattsson et al. (2010)	Clinical study	200 children with bladder dysfunction and inconti-nence	7.2	84 boys 116 girls	Urotherapy in small groups (2–5), called voiding school (VS)	At follow up at 3 and 12 months, 35% and 40% were cured and another 30% and 34% improved. Compared with the year before start of VS, urinary tract infections decreased from 34% to 6%.
Ma et al. (2017)	Randomized controlled trial	369 children with NE	8.00 ±2.77	216 boys 153 girls	Suoquan Desmopressin plus suoquan, Desmopressin, or behavioral intervention	Complete response rate: 37.5% in the desmopressin plus suoquan group, 22.5% in the desmopressin group, 6.3% in the behavioral intervention group. Relapse rate 72.2% in the desmopressin group and 30.6% in the desmopressin plus suoquan group.
Ma et al. (2019)	Clinical study	666 children with NE	6.5	349 boys 317 girls	Normal weight group Overweight group Obesity group	The rates of severe enuresis in patients with normal weight, overweight, and obesity were 63.9%, 77.5%, and 78.6%, respectively. The complete response of the normal group was higher than those of the overweight and obese groups (26.8% vs. 14.0%, P = 0.010; 26.8% vs 0.0%, P = 0.000). Overweight children showed higher complete response than obese ones (14.0% vs 0.0%, P = 0.009).
Alsharnoubi et al. (2017)	Randomized controlled trial	45 children with NE	Group A 9.43 ±2.77 Group B 8.8 ±3.18 Group C 9.93 ±3.16	Not mentioned	Group A desmopressin acetate Group B laser acupuncture Group C laser acupuncture and desmopressin	Higher cure rate in group B (73.3 %) than in groups A (20%) and C (13.3%)

used long-term without substantial risks, and side effects are rare, with higher incidence of complications under intranasal desmopressin therapy [16]. The main side effect is the risk of water intoxication (vomiting, headache, decreased consciousness, possible seizures, and hyponatraemia) if this medication is combined with excessive fluid intake [16]. Anticholinergics are the second-line antienuretic therapy; there are several anticholinergic drugs available with effectiveness proven in several studies, such as trospium chloride, solifenacin, and tolterodine, but only oxybutynin (0.1–0.3 mg/kg/d) is available for label use in children [17]. Oxybutynin performs its action by decreasing detrusor overactivity, a crucial factor in the pathogenetic mechanism of NE, especially in NMNE or enuresis nonresponsive to desmopressin therapy. It is not typically effective as monotherapy, so it can be added to desmopressin in children who experience daytime incontinence owing to urgency, as well as in patients who do not respond to desmopressin alone [24, 25]. The medication is taken in the evening one hour before bedtime and should be started with a dose in the lower interval 2.5–5 mg [17]. The favorable effect, if any, may not be immediately apparent, so the therapy should be evaluated after 1–2 months [17]. The most clinically relevant side-effects in the paediatric population are constipation (which may in turn influence LUT function), post-void residual urine, and dry mouth (which may lead to caries) [26]. Before considering anticholinergic treatment, constipation and residual urine need to be excluded: if initial therapeutic response is good but

the wet nights start to reappear, constipation should be suspected, and residual urine should be monitored once after 3–6 months. The tricyclic antidepressant imipramine, approved by the US Food and Drug Administration for the treatment of NE, is an evidence-based antienuretic therapy (evidence level Ia) that can be used as a third-line alternative [27]. It works by decreasing REM time, stimulating antidiuretic hormone secretion, and relaxing the detrusor muscle [28]. Among therapy-resistant enuretic children, 30–50% may be expected to benefit from imipramine, and this proportion increases if desmopressin is added [29]. Imipramine should be given approximately one hour before bedtime. The dosage is 25–50 mg with a therapeutic response after one month [17]. It has various side effects (anxiety, dizziness, drowsiness, lethargy, dry mouth, anorexia, vomiting), the most common and limiting in clinical practice being mood swings and nausea, but the more serious one is cardiotoxicity, which has limited the use of tricyclics in enuresis [30]. In the case of overdose or a child affected by unstable arrhythmia (long QT-syndrome), a fatal reaction may occur [31]. Thus, the drug should not be given without prior long-time electrocardiographic evaluation in case of positive anamnesis (history of unclear syncope/palpitations in the child, positive family history of sudden cardiac death). Few studies have studied the use of imipramine, usually in association with desmopressin. Ravanshad et al. investigated the efficacy of low-dose imipramine combined with desmopressin on the treatment of patients defined as desmopressin non-responders. Their analysis showed that low-dose imipramine is well tolerated in clinical practice and may represent a good short-term treatment option in combination therapy where desmopressin alone was not sufficient [32]. The noradrenergic drug mirabegron has recently proven to be an efficient and safe addition or alternative to anticholinergics in adults with detrusor overactivity, and future research could determine its possible role in children with enuresis [33]. An observation study by Kim et al. compared the efficacy and tolerability of mirabegron and solifenacin in paediatric patients with idiopathic overactive bladder. They reported a comparable efficacy of mirabegron to solifenacin in paediatric patients with drug-induced adverse effects in only 10% of the solifenacin-treated patients [34]. Moreover, in a recent multicentre study conducted in paediatric patients with neurogenic detrusor overactivity, mirabegron increased bladder compliance, bladder volume until first detrusor contraction, the average volume per catheterization, the maximum daytime catheterized volume, and the number of dry days per week, with a significant improvement in quality of life and

symptoms. Mirabegron seemed to be effective and well-tolerated in the treatment of paediatric patients with neurogenic detrusor overactivity, and it received its first approval in this indication in paediatric patients aged ≥ 3 years [35]. The combination therapy has been used in many clinical trials, especially in children resistant to desmopressin monotherapy, underlying the possibility of a major response and effectiveness in the case of multiple drugs. Esteghamati et al. conducted a randomized controlled trial to compare the efficacy of desmopressin plus tolterodine with desmopressin plus indomethacin in NE resistant to desmopressin monotherapy. They found that desmopressin plus tolterodine was superior, with complete response to treatment and lower treatment failure [36]. According to this, Kamperis et al. investigated the effect of combining indomethacin and desmopressin or desmopressin and placebo. Although the combination of indomethacin and desmopressin significantly reduced nocturnal urine output, it seemed to be ineffective in increasing dry nights in all children and in reducing enuresis frequency [37]. A trial conducted in 2021 in 62 patients with primary NE compared the therapeutic efficacy of the following treatments: solifenacin plus desmopressin, tolterodine plus desmopressin, and desmopressin alone. Although desmopressin has been used as a first drug, this study documented a higher response in combination therapy groups of desmopressin plus anticholinergic than the monotherapy group [38]. Austin et al. compared in a randomized controlled trial the use of combination therapy with desmopressin and an anticholinergic medication for non-responders to desmopressin. After one month of treatment, there was a significant reduction in the mean number of wet nights, with a significant 66% decrease in the risk of a wet episode, compared with the placebo group [39]. The implementation of anticholinergic agents may play an important role for a subset of children with enuresis who have a restricted bladder capacity and thickened bladder wall, as demonstrated by Montaldo et al., who assessed the efficacy of desmopressin plus oxybutynin in a randomized, double-blinded, placebo-controlled trial for 206 children with monosymptomatic NE (MNE) resistant to desmopressin [14]. Lee et al. confirmed this data by evaluating the efficacy of a combination of desmopressin and oxybutynin compared to the single drugs imipramine and desmopressin for treating children with NE. Combination therapy produced the best and most rapid results regardless of whether the children had monosymptomatic or polysymptomatic enuresis. Combination therapy with desmopressin plus oxybutynin for the treatment of paediatric NE was well

tolerated and gave significantly faster and more cost-effective results than single-drug therapy using either desmopressin or imipramine [40].

Non-pharmacological therapy

Enuresis alarm

Few treatments are empirically established for NE, and they are typically divided into pharmacological and non-pharmacological approaches [41]. Despite the pharmacological options, alarm treatment is still one of the main approaches used nowadays, with no side effects, a great rate of response and a success rate between 50% and 70% [42]. A clinical trial, conducted by Van Leerdam et al., reported a high success rate both in MNE and NMNE with a clinical improvement also 2 years after alarm treatment [43]. The full response in the long-term was described by Ozgür et al., who documented complete dryness in 32% (13/40) of patients at the end of a one-year period, although a relapse was observed in 66.7% [44]. Alarm treatment consists of a device that provides an arousal stimulus to the child and family when urine activates a detector placed in the child's bed or clothing [45]. Four forms of night alarms have been studied: sound, vibration, one that mixes an electrical impulse and a sound, and code words [46]. The use of acoustic stimuli, the most used, is configured in many ways with the same efficacy; it is associated with light or not, awakening the child immediately or after 3 minutes, putting a moisture sensor within the child's underclothing or just on the bed, alarming the parents or the child only [46]. The main aim of an enuresis alarm is to advise and educate the child to respond quickly and appropriately to a full bladder during sleep, transforming the signal from one of urination to that of inhibition of urination and waking [41]. Thus, the goal of an enuresis alarm is to train children to wake up for micturition before incontinence or to prevent emptying the bladder while asleep [47]. The mechanism of action of enuresis alarm systems is not fully understood, even if it is believed to involve amelioration of arousal in response to a full bladder. Taneli et al. in 2004 conducted a clinical trial on 28 children with MNE, evaluating the functional bladder capacity before and after a treatment period of 12 weeks. They documented a significant increase in bladder storage capacities (maximum nocturnal bladder capacity, maximum functional bladder capacity, and mean day-time bladder capacity) underlying that the effectiveness of alarm treatment is due not only to classical conditioning but it is also probably related to increases in bladder

storage capacities [48]. Other possible mechanisms have been studied by Butler et al., who hypothesized that, in a small sample of patients, dryness was achieved through a rise in osmolality in association with arginine vasopressin (AVP) release in children with NE and nocturnal polyuria (possibly lacking AVP release) and a rise in osmolality, with no change in AVP levels, in children with small bladder volumes (possibly overactive and with more concentrated urine) [49]. The most effective period of alarm treatment is about 16–20 weeks of continuous therapy, even if sometimes 2–3 months are considered enough for being dry for 14 consecutive days [46]. A randomized controlled trial, conducted by Kirill V Kosilov et al., compared the efficacy of alarm intervention after 12 weeks, 16 weeks, and 20 weeks. They documented the maximum effectiveness of treatment and the stability of long-term results after the range of time 16–20 weeks, maybe due to the formation of a neuroreflexive mechanism that created a habit for independent awakening in children with MNE [50]. Alarm therapy is considered the first treatment modality of choice for enuresis with a better treatment response, also in cases of relapse, and a lower recurrence rate as compared to other modalities of treatment [46, 47]. A meta-analysis by Pan Song et al. compared multiple treatments (desmopressin, alarm, desmopressin plus alarm, and desmopressin plus anticholinergic agent) in the management of MNE focusing on complete response and success rates. Although desmopressin plus an anticholinergic agent had higher success rates than desmopressin or alarm monotherapy, alarm therapy had the lowest relapse rate [51]. Naitoh et al. conducted a clinical trial in which they documented that the combination therapy with alarm and drugs for MNE was not superior to alarm monotherapy, considering multiple therapy as a second choice in the case of non-response [52]. The relapse rate was assigned to family situation, behaviour deviance in the child, and the educational level of the parents. The variable length of enuresis alarm was associated with a dropout rate of 10–30% [45]. A motivated child and compliance of the family, who must be totally informed in a comprehensive manner, is a critical favourable prognostic indicator for alarm therapy, as declared by the International Children's Continence Society [43]. It is demonstrated by a wide range of trials such as the study by Tsuji et al. that demonstrated a similar efficacy both in children awakened by family members and in children self-responsible for waking to the alarm [53]. Sleep deprivation and behavioural problems, such as attention deficit hyperactivity disorder (ADHD), are prognostic factors to be considered [43].

Dietary Intervention

Diet changes, including reduced fluid intake before bedtime, reduced consumption of foods and drinks containing caffeine, reduced consumption of carbonate drinks, are usually recommended in recent years, because it has been established that some foods and beverages can promote diuresis or detrusor over-activity [54, 55, 56]. For example, restricted fluid intake after 6 p.m. (or 3–4 h before bedtime) may reduce the total overnight urine production and thus the child's need to void overnight. Carbonated drinks and artificial sweeteners may contribute to overactive bladder symptoms while caffeine also has a diuretic effect [57]. Ferrara et al. listed recommended and non-recommended foods in children with NE [57]:

- Recommended foods: vegetables, fish, seafood, dried fruits, cereals, and eggs
- Non-recommended foods: salt, chocolate, cocoa, carbonated drinks, tea, and fruit juice
- Non-recommended foods in the evening: fruit, water, yogurt, cheese, and milk.

Dietary recommendations are based on pharmacological and clinical studies underlying possible mechanisms of NE pathophysiology. Nikibakhsh et al. considered hypercalciuria an important pathogenic factor of NE because it seems to decrease the amount of aquaporin-2 detectable in the urine, and urinary excretion of AQP2 in humans has been proposed as a potential marker of collecting-duct responsiveness to vasopressin. Moreover, hypercalciuria seems to be correlated with desmopressin resistance [58]. Thus, Ferrara et al. did not recommended ripened cheese, such as parmesan cheese, grana Padano, and pecorino (Italian sheep cheese) at every meal because aged cheeses were too rich in calcium, and they recommended vegetables rich in oxalate and phytate that inhibit bowel calcium absorption [57]. Evidence of lower levels of vitamin B12 and folate in enuretic chil¬dren, maybe involved in neurogenic maturation and nocturnal bladder control, led to the suggestion of eating foods rich in them such as meat, fish, albumen and yolk, seafood, wheat germ, wheat bran, corn flakes, crisped rice, asparagus, and turnip greens [57, 59]. However, clinical trials and a larger sample of enuretic children are needed to establish the effectiveness of diet advice.

Pelvic floor retraining

Pelvic floor rehabilitation is a behavioural and exercise-based treatment approach to NE, firstly introduced as a specific urotherapy by Wennergren and Oberg to increase children's awareness of their pelvic floor muscles and its contraction and relaxation [60]. The use of pelvic floor retraining is based on the hypothesis that NE, but also daytime incontinence, in children may be due to muscle overactivity and ligament weakness that destabilize control of the micturition reflex [61]. Despite the larger implementation in NE management, no exercise protocol has been standardized, with variations in the number of repetitions, duration of contraction and relaxation, and period of training. A trial conducted by Campos et al., including children with NE and other lower urinary tract symptoms, compared standard urotherapy alone with pelvic floor muscle training alone and in combination with oxybutynin. Standard urotherapy consisted of behavioural modification, proper voiding posture, bowel habits, and voiding intervals at every 2 hours, while pelvic floor exercises were 2 series of 10 maximal effort pelvic floor muscle contractions, totalling 20 contractions per session with a electromyography biofeedback. They showed no difference in treatment results, also after 2 years, documenting that all treatment modalities were effective regarding improved enuresis and lower urinary tract symptoms [62]. Vesna et al. reported after one year of therapy a significantly larger number of cured children, who suffered from urinary incontinence and NE, if subjected to diaphragmatic breathing and pelvic floor muscles, while Van Kampen et al. established no beneficial effect of including pelvic floor muscle training in full-spectrum therapy [59, 63, 64]. Squatting and diaphragmatic breathing exercises are the main protocols used. Squatting-based pelvic floor exercises are based on the results of Petros et al. in a premenopausal adult population, in whom they strengthened involuntary pelvic muscles and the ligaments they contracted against, with improvement of nocturia, stress urinary incontinence and bowel symptoms in 70–90% of premenopausal women [65]. Garcia-Fernandez et al. evaluated the role of squatting exercises, compared with a control group in which children ran 50 metres in the morning and at night, in children with NE after 4 weeks and 4 months of treatment. Squatting exercises included 10 squats morning and evening at home, 10 bridge exercises morning and evening at home, and fitball exercises involving pelvic anteversion and retroversion once a week, which involved proprioception exercises with surface perineal electromyography. At 4 weeks 12/24 in the treatment group reported total cure of wetting while 41/48 children (86%) were cured of both daytime/nighttime enuresis at 4 months [66].

Diaphragmatic breathing is an exercising technique to help strengthen the diaphragm. In a lying or sitting position, children are asked to inhale the air through the nose, bulge the abdomen outwards as

much as possible, hold their breath for a few seconds, and then exhale slowly through pursed lips.

Children are asked to watch the anterior abdominal wall movement during inspiration and repeat the same action when they start voiding. Zivkovic et al. conducted research in children with dysfunctional voiding to investigate the function of abdominal and pelvic floor training. After one year of therapy, most children did not present urinary incontinence, NE, and urinary tract infections: urinary incontinence was cured in 20 out of 24 patients (83%), and NE in 12 out of 19 children (63%) [66]. Despite the controversial results, pelvic floor rehabilitation remains an effective, inexpensive, and simple tool to integrate into the management of NE [67].

Bladder training

According to the International Children's Continence Society, standard therapy or basic bladder advice (BBA) includes a wide range of interventions such as education, lifestyle changes, registration of symptoms, and support for the child and the family to optimize voiding patterns and improve bladder dysfunction such as enuresis [68, 69]. Although fewer trials have studied BBA in enuretic children, with strong evidence especially in children with day-time voiding problems, it is recommended as first-line therapy against enuresis regardless of the underlying condition [70].

Recent clinical trials have shown limited efficacy of BBA, mostly pronounced after the third month of therapy, while other studies supported its effectiveness and good response, with about a third of children responding to standard therapy alone [68, 70, 71]. Moreover, the duration of BBA as monotherapy and its efficacy in MNE is still a matter of debate. The duration of BBA in the study by Cederblad et al. was one month, with a complete response in 5% of children, while in the study of Kajbafzadeh et al. and Hascicek et al., with 2 months of therapy, the response rates were 25% and 30%, respectively [72, 73, 74]. Thus, a longer time window is recommended for a higher rate of response. The intensity of the intervention regimen might affect the response. Hascicek et al. documented that the implementation of a written checklist of behavioural instructions improved therapy and its effectiveness, while Mattsson et al. enrolled 200 children with bladder dysfunction and incontinence to participate in voiding schools in small groups, a multidisciplinary combined in- and outpatient bladder rehabilitation program, with higher response rate [74, 75]. Efficacy of urotherapy might be influenced by predictive factors such as gender, age (higher compliance and response

in older children), maternal education level, frequency of symptoms, overweight, and obesity [76, 77]. Despite the conflicting available data, low cost, and lack of risk make urotherapy a first-line treatment in NE, it might more efficient as an add-on to other first-line treatments instead of an independent intervention.

Acupuncture

Acupuncture has been used as a primary therapy for NE, especially in Asia, with evidence from clinical trials and systematic reviews of positive effects, despite a great heterogeneity, suggesting that some forms of acupuncture might be more effective than others, and disparate results from similar interventions [78]. Acupuncture is based on the theory of 12 primary meridians or energy channels along which are distributed 360 acupuncture points. The sites used to treat bladder dysfunction coincide with innervation by spinal sacral segments S2 through S4, and the stimulation of these acupoints (manual pressure, penetration of the skin, heating, the application of laser, electrotherapy, or moxibustion) should cause homeostatic changes [78]. A comparative study conducted by Alsharnoubi et al. evaluated the effect of using laser acupuncture and medication for the treatment of children with NE. They documented a significantly higher cure rate of about 73.3%, in children subjected to laser acupuncture, while response to traditional therapy was about 20% [79]. However, although acupuncture is a noninvasive painless tool, it is not suggested by clinicians and not recommended in guidelines.

Complementary interventions

Other treatments have been considered in NE, but they are not recommended because they have insufficient data to recommend their use in children with NE, based mostly on the poor quality of the data available for analysis. A Cochrane review conducted in 2005 investigated psychotherapy and counselling, suggesting their use in the management of children with psychological problems in addition to enuresis. On the other hand, hypnosis and homeopathy are not included in the recent guidelines and are considered as less traditional approaches used to treat bedwetting [80]. These alternative therapies need more data from quality randomized trials, but they may be incorporated in a more complex treatment plan for refractory children.

In severely therapy-resistant enuresis, the endoscopic injection of botulinum toxin and sacral neurostimulation have been studied as alternative treatments,

even if they are not recommended as first- and second-line treatments because of the lack of evidence and randomized clinical trials. A pilot study by Jung et al. including 27 patients with NME, who showed no response after conservative treatment for more than 12 months, documented an improvement of detrusor overactivity after intravesical botulinum toxin injection up to one year later, while Hoebeke et al. reported positive long-term results in 70% of children after a single injection [81, 82]. There are limited data on the effectiveness of sacral nerve stimulation in children. A clinical trial by Humphreys et al. studied the effectiveness of sacral nerve stimulation in children affected by urinary symptoms (dysfunctional voiding, enuresis, incontinence, urinary tract infections, bladder pain, urinary retention, urgency, frequency) and bowel symptoms. The study documented an improvement of urinary incontinence in 84%, improvement of enuresis in 69%, and improvement of urinary retention in 60% [83]. Sacral neuromodulation via implanted pulse generator, as a treatment for children with dysfunctional elimination syndrome and symptoms refractory to maximum medical therapy, has been studied in the 10-year single-centre experience by McCrery et al., showing an improvement of urinary incontinence, constipation, frequency and/or urgency, and enuresis [84]. However, larger samples and randomized clinical trials are required to understand and assess the use of botulinum toxin injection and nerve stimulation in enuresis treatment. Moreover, a multidisciplinary approach is recommended because comorbidities are one of the main factors to be considered in the global management of NE, as demonstrated by clinical studies in which their improvement reduced NE severity and improved treatment response [85–88]. For example, Juszczak et al. reported obstruction of the upper airway tracts, causing sleep apnoea and other breathing abnormalities, as a predictive factor in NE, as well as the positive effect of maxillary expansion on reducing bedwetting symptoms [89]. This evidence was based on previous studies, such as one by Oshagh et al., who documented in a preliminary study the reduction of the frequency of wetting during the period of appliance of slow maxillary insertion without expansion. During the expansion and retention phase, 2 patients became completely dry, and 2 patients improved significantly [90]. Sleep dysregulation and constipation are the other 2 main comorbidities affecting NE. Several studies have already shown that a wide range of comorbidities influence the prognosis and the response to the therapy in enuretic children [85–94].

CONCLUSIONS

NE is a common health problem. Different medical disciplines deal with children with enuresis and their families: paediatrics, paediatric nephrology, and paediatric urology, in addition to child psychology and child psychiatry, urotherapists, and others. Multiple treatment approaches, both pharmacological and non-pharmacological, have been established and validated by the ICCS to reduce signs and symptoms of NE and improve quality of life and the social and emotional discomfort experienced by children. The aim of paediatricians is to identify the right therapy protocol for very single child, evaluating the best approach for the child and their family. Overall, all the pharmacological and non-pharmacological approaches to NE appear to be useful, with the latest innovative approaches looking promising even if further randomized clinical trials including a wide range of patients are necessary to validate these methods and develop standardized protocols shared in the scientific community.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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