Journal of Pediatric Urology (xxxx) xxx xxx

Original Research

Ginkgo biloba versus desmopressin in treatment of children with monosymptomatic nocturnal enuresis: A randomized controlled trial

Mohamed El-Shazly [a], Ammar Alorabi [a,*], Ibrahim E. Alahmar [b], Ibrahim Gomaa [a], Mohammed Aziz [a], Khaled Magdy Zeinelabden [c]

[a]Urology department, Faculty of medicine, Menoufia University, Shibin el Kom, Egypt

[b]Neuropsychiatry department, Faculty of medicine, Menoufia University, Shibin el Kom, Egypt

[c]Urology department, Faculty of medicine, Kafrelsheikh university, Kafrelsheikh, Egypt

* Correspondence to: Ammar Alorabi, Urology department, Faculty of medicine, Menoufia University, Shibin el Kom, Egypt
mshazly2001@yahoo.com (M. El-Shazly)
ammar.alorabi95@gmail.com (A. Alorabi)
ibrahim_mowafy_298@yahoo.com (I. Gomaa)
mohamed.aziz@med.menofia.edu.eg (M. Aziz)
ddrkhaled@yahoo.com (K.M. Zeinelabden)

Keywords
Monosymptomatic nocturnal enuresis; Ginkgo biloba; Ginkgo biloba extract; Desmopressin; Quality of life

Abbreviations
MNE, Monosymptomatic Nocturnal enuresis; QoL, Quality of Life; PinQ, the Pediatric incontinence Quality of life questionnaire; EAU, European Association of Urology; ICCS, International Children's Continence Society; GBE, Ginkgo Biloba Extract; SDSC, Sleep Disturbance Scale for Children; DA, Disorders of Arousal

Received 13 January 2026
Revised 25 April 2026
Accepted 2 June 2026
Available online xxx

Summary

Objective
To evaluate the efficacy and safety of Ginkgo biloba extract (GBE) compared with Desmopressin and their combination in children with monosymptomatic nocturnal enuresis (MNE).

Methods
In this double-blind, randomized, placebo-controlled trial, 398 children aged 5–14 years with MNE were assigned to four groups: placebo, GBE (60 mg daily), Desmopressin (0.2 mg daily), or GBE plus Desmopressin for 3 months. Primary outcomes included the number of wet nights per week. Secondary outcomes assessed sleep quality using the Sleep Disturbance Scale for Children (SDSC), arousal by the Disorders of Arousal (DA) score, and quality-of-life using the Pediatric Incontinence Questionnaire (PinQ).

Results
After 3 months, the combination group demonstrated the greatest improvement in wet nights (median 0 [IQR 0–2]) compared to GBE (6 [0.5–6.5]) and Desmopressin (2 [0–6]) ($p < 0.001$). Full response rates (≥90% reduction in wet nights) were highest with combination therapy (88.3%), followed by Desmopressin (46.5%), GBE (24.8%), and placebo (9.5%) ($p < 0.001$). GBE-containing groups showed significantly increased DA and SDSC scores, indicating enhanced arousal and lighter sleep. Quality-of-life (PinQ) score decreased in all treatment groups denoting improvement, with the best outcomes observed in the combination arm. Adverse effects were mild and comparable across groups, and serum sodium levels remained stable.

Conclusion
GBE is a safe and effective novel therapy for MNE, improving sleep arousal and symptom control. Its combination with Desmopressin offers superior efficacy, better quality of life, and lower relapse rates than either agent alone.

Introduction

Monosymptomatic nocturnal enuresis (MNE) is involuntary bed wetting during sleep in children older than 5 years old, MNE is considered one of the most socially stigmatizing and distressing medical problems which occurs in 15%–20% of five year old children, affecting the quality of life (QoL) of both children and parents [1]. Since MNE is a health-related QoL disease, QoL is believed to be evaluated using standardized tools [2]. The Pediatric Incontinence Quality of Life (PinQ) questionnaire is a validated tool designed to assess the impact of urinary incontinence on a child's daily life, emotions, and social well-being. It helps clinicians and researchers measure how incontinence affects QoL from the child's perspective [3].

According to the European Association of urology (EAU) guidelines 2025, either Desmopressin or a combination of Desmopressin and an anticholinergic drug are considered the mainstay medical treatment for management of MNE, beside supportive measures and wetting alarm treatment [4]. Desmopressin has been accounting for success rate of 70% with a favorable safety profile of rare preventable adverse effects such as water intoxication [5].

According to The International Children's Continence Society (ICCS) the alarm therapy and Desmopressin is considered the first-line for MNE treatment [6]. Alarm therapy modulates the patient arousal response to urinary

https://doi.org/10.1016/j.jpurol.2026.106077

bladder [7]. While Desmopressin reduces nocturnal urine production.Despite Desmopressin proven efficacy but it is associated with higher relapse rates in children with sleep arousal disorders [8].

As one of the contributing factors to MNE is sleep disorder with an inability to wake up when in need to pass urine at night [9]. Ginkgo Biloba extract (GBE) and its components, such as Ginkgolide B, are thought to promote wakefulness and reduce non-rapid eye movement sleep by negatively modulating GABA and glycine activity at their respective receptors (GABAA and glycine receptors) [10]. GBE has many pharmaceutical applications including cardiovascular disorders, premenstrual syndrome, memory, Alzheimer's disease [11]. However, it has not been evaluated as a line of management for MNE.

Regarding literature, GBE in children, it seems to be well tolerated and safe with no significant side effects in children between 4yrs and 12yrs old [12]. This study aimed to evaluate the efficacy and safety of GBE as monotherapy or in combination with Desmopressin as a novel treatment of MNE, using a prospective, double-blinded, randomized trial.

Patient and methods

This prospective, randomized, double-blind, placebo-controlled study was carried out on 398 children with MNE at two tertiary centers in the period from November 2024 to December 2025.

Written informed consent was obtained from parents and informed about the treatment and side effects of each medication. The study protocol was approved by the Ethical Committee of our local university before participant recruitment and was registered retrospectively on clinicaltrials.org under the number (NCT06771128). Steps adhered to the principles of the Declaration of Helsinki. Children with the eligibility criteria were recruited consecutively from urology outpatient clinics at both centers.

We included all children aged 5—14 years diagnosed with primary MNE based on ICCS criteria, enuresis without other LUT symptoms with no previous dry period of >6 months [13], with normal physical examination and laboratory tests, with no history of treatment for MNE in the previous 3 months. Any child with non-monosymptomatic enuresis or any daytime lower urinary tract symptoms, nocturia, congenital urinary tract anomalies, diabetes mellitus or diabetes insipidus, neurological disorders, psychiatric illness, or current use of medications that may affect sleep or bladder function was excluded. Children were assessed primarily using a 7-day bladder diary with documentation of maximum voided volume (MVV) and any child with MVV of <65% or >150% of expected bladder capacity is considered abnormal bladder capacity and thus abnormal bladder function then excluded. Participants were randomly divided into four groups using a computer-generated randomization sequence. To maintain allocation privacy, sequentially numbered, opaque, sealed envelopes (SNOSE) were used. Randomization was performed by an independent statistician with no clinical involvement.

Children, parents, urologist, nurse, data collector, and outcome evaluation doctor were all blinded to group assignments. Medications (GBE and Desmopressin) and their matched placebo were similar in color (white), size, shape, labeling and packaging film-coated, minimizing taste differences and composed of starch. Only the pharmacy unit had access to the allocation list and dispensing coded medication packs. To achieve the double-blind design, patients of each group were given a combination of 2 tablets with the content of each tablet follows the assigned group and known only by the pharmacy unit.

The four groups were: Group 1 (Placebo, n = 95): Received 2 placebo tablets (pharmaceutical-grade starch) once daily which was similar in appearance to both GBE and Desmopressin tablets, Group 2 (GBE, n = 101): Received oral GBE 60 mg + placebo tablet once daily, Group 3 (Desmopressin, n = 99): Received oral Desmopressin 0.2 mg + placebo tablet once daily, and Group 4 (Combination therapy, n = 103): Received both Desmopressin 0.2 mg and GBE 60 mg.

The dose of GBE was determined based on previous studies using GBE for treatment of ADHD in children [14]. We used minimal mentioned dosage to ensure safety of the used drug. GBE tablets were film-coated to minimize taste differences. placebos were prepared by the hospital pharmacy to match the original drug in appearance and flavor only and used as needed to maintain blinding regarding the number and appearance of tablets. For 3 months, all medications were administered at bedtime with fluid restriction applied according to desmopressin guidelines. All medications were provided via the hospital pharmacy with no specific trade names and covered by patients' medical insurance.

Assessment of primary outcome depended on number of wet nights per week, evaluated using a 7-day bladder diary at baseline, 1 month, and 3 months, while secondary outcomes included the assessment of Sleep Disturbance Scale for Children (SDSC) (which is 26-item validated measure; score range: 26—130, Higher scores indicate lighter sleep), Disorders of Arousal Score (DA Score) (which is a sub-score of SDSC and focus on evaluation of sleep arousal disorder, higher scores indicate better arousal), and PinQ (which is a Validated QoL tool (score range 20—80) Higher scores indicate worse QoL).

Enuresis Severity was graded as follows: Mild ≤3 wet nights/week, Moderate = 3—5 wet nights/week and Severe ≥6 wet nights/week. Serum sodium levels were measured via morning samples at baseline, at 1 week and 1 month given safety considerations with Desmopressin use.

Parents completed a 7-day bladder diary before each assessment visit. SDSC and DA scores were evaluated by urologists. PinQ questionnaires were completed by children with parental assistance. Adverse events and treatment-related side effects were documented at each follow-up visit. Relapse rate was assessed after treatment discontinuation at 3 months via assessment of enuresis frequency and PinQ score.

Statistical analysis

One-way ANOVA was used for normally distributed continuous variables (SDSC, DA scores, serum sodium). Kruskal—Wallis test was used for non-normal variables (wet

Please cite this article as: El-Shazly M et al., Ginkgo biloba versus desmopressin in treatment of children with monosymptomatic nocturnal enuresis: A randomized controlled trial, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2026.106077

nights, PinQ scores). Chi-square test was used for categorical variables (sex distribution, severity categories). Repeated measures ANOVA and Friedman test were used for within-group comparisons over time. Post-hoc pairwise analyses were conducted following significant omnibus tests. Statistical significance was set at $p < 0.05$ and $p \leq 0.001$ was considered highly significant.

Results

After exclusion of 21 out of 436 children with MNE due to ineligibility, a total of 415 children were randomized and allocated to four nearly equal groups. Across all groups, twelve patients were lost to follow up and five discontinued interventions. Finally, a total of 398 children with MNE were enrolled and randomized into four treatment arms: placebo ($n = 95$), GBE ($n = 101$), Desmopressin ($n = 99$), and combination therapy ($n = 103$) as demonstrated in CONSORT flowchart (Fig. 1).

Regarding the baseline criteria, there were no statistically significant differences among the studied groups with respect to age ($p = 0.803$), sex distribution ($p = 0.99$), BMI ($p = 0.452$), baseline number of wet nights/week ($p = 0.689$), enuresis severity ($p = 0.827$), SDSC score ($p = 0.418$), DA score ($p = 0.166$), PinQ score ($p = 0.550$), or serum sodium level ($p = 0.654$) (Table 1).

Regarding number of wet nights per week, there was a strong and significant difference between the groups at both 1 and 3 months ($p < 0.001$). After 1 month, there was a significant difference between all groups; The placebo group had the most wet nights (median 6), while the combination group had the least one while after 3 months, the placebo group showed only slight improvement, while the combination therapy continued to show the best results and also all pairwise comparisons were significant. Within groups, every group showed significant improvement over time ($p < 0.001$) (Table 2).

Regarding SDSC score, group differences became significant at both follow-up points ($p < 0.001$). SDSC scores were highest in the combination group, and group 2 (GBE) also showed higher scores than placebo. Within groups, SDSC scores increased significantly in all groups, with the largest increases in Ginkgo-containing groups indicating lighter sleep in such groups (Table 2).

Regarding DA Score, significant differences were found at 1 and 3 months ($p < 0.001$). Children receiving GBE or combination therapy had better DA scores than those on placebo or Desmopressin. Within groups, DA improved significantly in groups 2 and 4 while no significant change occurred in groups 1 and 3 (Table 2).

Regarding PinQ Score, there were highly significant differences between groups at 1 and 3 months ($p < 0.001$). After 1 month, all groups differed significantly except placebo vs. GBE. After 3 months, all comparisons were significant. The combination therapy group showed the greatest reduction in PinQ score indicating better QoL. Within groups, all groups improved significantly over time ($p < 0.001$) (Table 2).

Regarding therapeutic response rates, there was a strong difference in treatment response at both 1 and 3 months ($p < 0.001$). Full Response ($\geq$90% improvement) was recorded after 1 month as follows; Placebo (4.2%), GBE (16.8%), Desmopressin (35.4%), and Combination (51.5%).

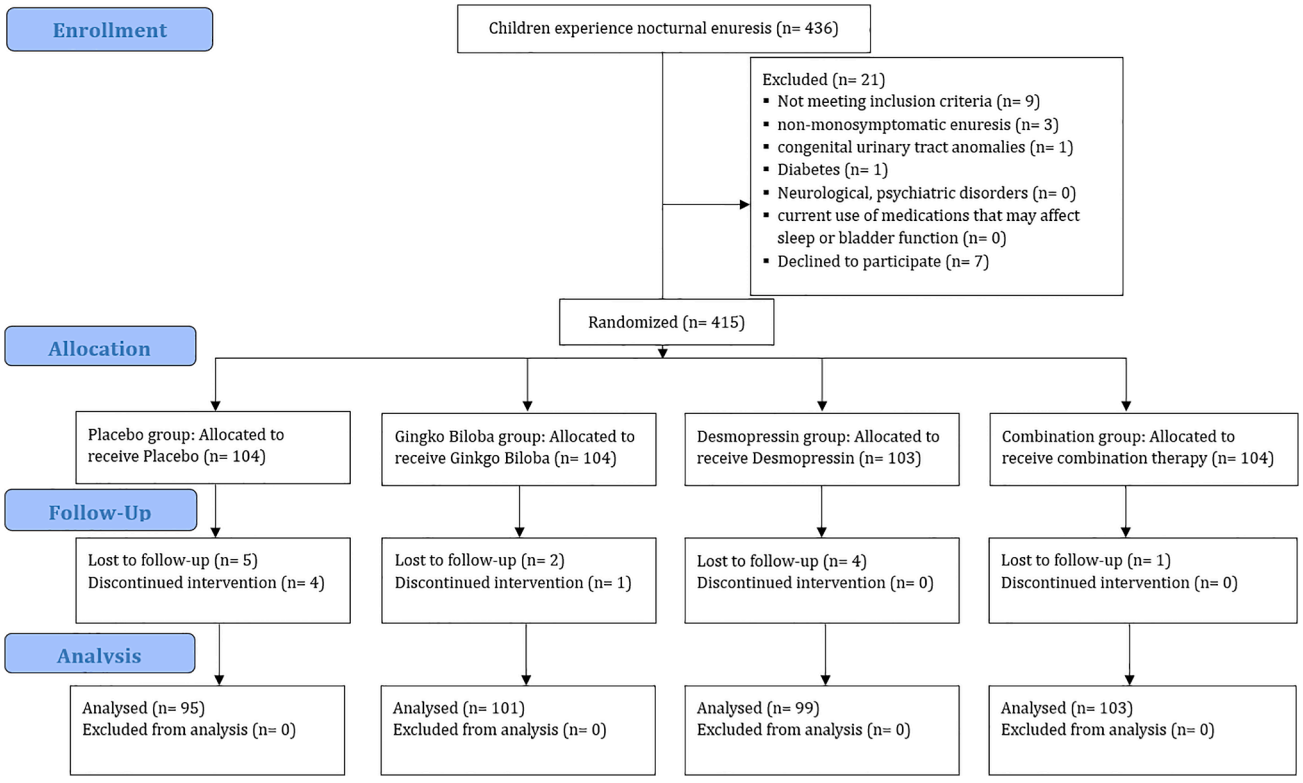

Figure 1 CONSORT flowchart.

Please cite this article as: El-Shazly M et al., Ginkgo biloba versus desmopressin in treatment of children with monosymptomatic nocturnal enuresis: A randomized controlled trial, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2026.106077

Table 1 Comparison between the studied groups regarding demographic and baseline data.

	Group 1 (placebo)	Group 2 (GBE)	Group 3 (Desmopressin)	Group 4 (combination therapy)	p- value
Demographic data					
Age[a]	10.11 ± 2.12	10.36 ± 2.16	10.31 ± 2.16	10.39 ± 2.29	0.803
Sex					
Male	72 (75.8%)	75 (74.3%)	73 (73.7%)	77 (74.8%)	
Female	23 (24.2%)	26 (25.7%)	26 (26.3%)	26 (25.2%)	0.990
BMI[a]	23.46 ± 3.0	24.13 ± 3.5	23.95 ± 3.41	24.14 ± 3.35	0.452
Baseline data					
Number of wet nights per week[b]	6(6—7)	6(6—7)	6(6—7)	6(6—7)	0.690
Severity					
Moderate	8 (8.4%)	10 (9.9%)	10 (10.1%)	7 (6.8%)	
Severe	87 (91.6%)	91 (90.1%)	89 (89.9%)	96 (93.2%)	0.827
SDSC score[a]	43.02 ± 5.12	43.48 ± 5.13	44.01 ± 4.88	44.06 ± 4.82	0.418
DA score[a]	4.46 ± 1.16	4.45 ± 1.41	4.82 ± 1.37	4.47 ± 1.43	0.166
PinQ score[b]	41(30—54)	42(29—56)	45(31—55)	47(34—56)	0.550
Na level[a]	139.8 ± 3.13	140.06 ± 3.1	140.35 ± 3.29	139.95 ± 3.05	0.654

[a] Data is represented as mean ± SD and compared using one way ANOVA test.
[b] Data is represented as median and interquartile range and compared using Kruskal Wallis test data is represented as number and % and compared using Chi square test.

While after 3 months; Placebo (9.5%), GBE (24.8%), Desmopressin (46.5%), and Combination (88.3%) which was the highest. All pairwise comparisons were significant (Table 2).

The combination therapy group had significant non-responders, only 7.8% at 3 months compared to other groups. Within groups, all groups showed a significant increase in full responders over time ($p < 0.05$) (Table 2).

Regarding relapse rate, there was statistically significant difference between the studied groups ($p < 0.001$). On doing pairwise comparison, difference was significant between combination group and each other group (relapses were significantly low in combination group). According to the adverse effects and sodium level changes, there were no statistically significant differences between groups at 1 week and 1 month (Table 3). No vasoactive adverse effects, hypotension or headache were reported.

Discussion

This is a randomized, double-blind, placebo-controlled trial which evaluated GBE as a novel treatment either as monotherapy or in combination with Desmopressin in management of MNE.

Desmopressin remains a first-line treatment of MNE due to its ability to reduce nocturnal urine production [15]. Despite overall response rates of 60—70%, only approximately one-third of patients achieve full response, while a considerable proportion demonstrate partial or no improvement [16,17]. As MNE involves multiple factors such as nighttime urine volume production, bladder function, and impaired arousal, Desmopressin use as monotherapy might be limited specially in refractory cases and also limited by safety concerns, particularly the risk of low sodium which may require fluid restriction [17].

For Desmopressin non-responders, combination therapy with anticholinergics is commonly used as second-line treatment. While anticholinergics can improve bladder capacity and reduce urgency by targeting detrusor overactivity [18,19], their use is limited by the cumulative "anticholinergic burden," including gastrointestinal, autonomic, and cognitive adverse effects [20—22].

A defining criterion of MNE in many children is an elevated arousal threshold during sleep, resulting in failure to awaken in response to bladder filling despite normal bladder function and controlled urine volume. The therapeutic rationale for GBE depends on its central neuropharmacological properties. Experimental evidence demonstrates that GBE constituents, particularly terpene trilactones and ginkgetin, antagonize inhibitory γ-aminobutyric acid (GABAA_AA) and glycine receptors, thereby reducing central inhibitory tone and facilitating cortical arousal [23,24].

Preclinical and translational studies further support this mechanism, showing that ginkgetin modulates sleep pattern and affects REM and NREM transitions, consistent with wakefulness-promoting effects [25]. Additionally, GBE has demonstrated neurobehavioral effects in many pediatric neuropsychiatric conditions, including improved attention, reduced irritability, and enhanced cognitive control [12,26,27].

In the present study, baseline data across treatment groups confirmed successful randomization. Outcome assessment not only depended on wet-night frequency but also included validated patient-reported (PinQ) and measured (SDSC and DA scores), enhancing both clinical and pathophysiological interpretation [3].

Secondary outcomes showed the direct GBE's central action. GBE-containing groups showed statistically significant increase in SDSC and DA scores, indicating lighter sleep, increased arousal and reduced daytime attention. These findings represent the pharmacologic consequence of arousal enhancement as GBE mostly acts on the neurophysiological level.

Please cite this article as: El-Shazly M et al., Ginkgo biloba versus desmopressin in treatment of children with monosymptomatic nocturnal enuresis: A randomized controlled trial, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2026.106077

Table 2 Comparison between the studied groups regarding outcomes at baseline, after 1 month and after 3 months.

	Group 1 (placebo)	Group 2 (GBE)	Group 3 (Desmopressin)	Group 4 (combination therapy)	p-value
Number of wet nights per week [d] *[median (IQR)]*					
Baseline	6(6–7)	6(6–7)	6(6–7)	7(6–7)	0.166
After 1 month	6(6–7) [h,i,j]	6(2–7) [g,i,j]	2(0–6) [g,h,j]	0(0–3) [g,h,i]	<0.001 [f]
After 3 months	6(3–7) [h,i,j]	6(0.5–6.5) [g,i,j]	2(0–6) [g,h,j]	0(0–2) [g,h,i]	<0.001 [f]
p [a]	<0.001 [f]	<0.001 [f]	<0.001 [f]	<0.001 [f]	
SDSC score [c] *[mean ± SD]*					
Baseline	43.02 ± 5.12	43.48 ± 5.13	44.01 ± 4.88	44.06 ± 4.82	0.418
After 1 month	43.4 ± 5.02 [h,j]	45.53 ± 5.91 [g]	44.48 ± 5.2 [j]	46.72 ± 5.3 [g,i]	<0.001 [f]
After 3 months	43.59 ± 5.25 [h,j]	45.85 ± 5.81 [g]	44.69 ± 5.25 [j]	47.2 ± 5.27 [g,i]	<0.001 [f]
p [b]	<0.001 [f]	<0.001 [f]	<0.001 [f]	<0.001 [f]	
DA score [c] *[mean ± SD]*					
Baseline	4.46 ± 1.16	4.45 ± 1.41	4.82 ± 1.37	4.47 ± 1.43	0.166
After 1 month	4.58 ± 1.4 [h,j]	6.25 ± 2.26 [g,i]	4.66 ± 1.69 [h,j]	6.76 ± 2.1 [g,i]	<0.001 [f]
After 3 months	4.77 ± 1.59 [h,j]	6.59 ± 2.23 [g,i]	4.86 ± 1.92 [h,j]	7.24 ± 1.74 [g,i]	<0.001 [f]
p [b]	0.077	<0.001 [f]	0.061	<0.001 [f]	
PinQ score [d] *[median (IQR)]*					
Baseline	41(30–54)	42(29–56)	45(31–55)	47(34–56)	0.55
After 1 month	36(24–51) [i,j]	29(19–50.5) [i,j]	21(15–39) [g,h,j]	16(14–24) [g,h,i]	<0.001 [f]
After 3 months	30(21–48) [h,i,j]	24(16.5–47) [g,i,j]	19(14–29) [g,h,j]	14(12–16) [g,h,i]	<0.001 [f]
p [a]	<0.001 [f]	<0.001 [f]	<0.001 [f]	<0.001 [f]	
Types of response after 1 month and after 3 months					
Children with full response					
After 1 month	4 (4.2%) [h,i,j]	17 (16.8%) [g,i,j]	35 (35.4%) [g,h,j]	53 (51.5%) [g,h,i]	
After 3 months	9 (9.5%) [h,i,j]	24 (24.8%) [g,i,j]	46 (46.5%) [g,h,j]	91(88.3%) [g,h,i]	
Children with partial response					
After 1 month	10 (10.5%) [h,i,j]	15 (14.9%) [g,i,j]	25 (25.3%) [g,h,j]	26 (25.2%) [g,h,i]	
After 3 months	15 (15.8%) [h,i,j]	20 (19.8%) [g,i,j]	22 (22.2%) [g,h,j]	4 (3.9%) [g,h,i]	
Children with no response					
After 1 month	81 (85.3%) [h,i,j]	69 (68.3%) [g,i,j]	39 (39.4%) [g,h,j]	24 (23.3%) [g,h,i]	
After 3 months	71 (74.7%) [h,i,j]	56 (55.4%) [g,i,j]	31 (31.3%) [g,h,j]	8 (7.8%) [g,h,i]	
p-value	0.004 [e]	<0.001 [f]	<0.001 [f]	<0.001 [f]	

[a] P, for Friedman test.
[b] p, for repeated measure ANOVA test.
[c] Data is represented as mean ± SD and compared using one way ANOVA test.
[d] Data is represented as median and interquartile range and compared using Kruskal Wallis test data is represented as number and % and compared using Chi square test.
[e] $p < 0.05$ is statistically significant.
[f] $p \leq 0.001$ is statistically highly significant.
[g] significant compared to group 1.
[h] significant compared to group 2.
[i] significant compared to group 3.
[j] significant compared to group 4.

GBE monotherapy produced a significant full-response rate, confirming impaired arousal as an independent and therapeutically modifiable pathway in MNE. Desmopressin monotherapy demonstrated superior efficacy through volume control; however, the most important finding was the synergistic effects of combination therapy which targeting both urine volume reduction (Desmopressin) and central arousal (GBE) produced significant response rates reported for MNE treatment, improving outcomes achieved with traditional therapy [16].

All active treatment groups demonstrated significant improvements in health-related QoL, as measured by PinQ, with the greatest benefit observed in the combination group.

GBE represents an alternative to anticholinergic agents. Unlike muscarinic antagonists, which primarily target bladder smooth muscle, GBE directly acts on the neurological arousal deficit without any anticholinergic side effects [12]. This makes GBE may be used as treatment option for children in whom impaired arousal is the dominant pathophysiological factor in MNE.

Previous studies have also shown that combination therapy was effective as it is targeting both the physiological (nocturnal polyuria) and behavioral (arousal training) components of MNE [28,29]. The placebo effect was observed to have lower response compared to the previous studies which may be due to higher compliance

Please cite this article as: El-Shazly M et al., Ginkgo biloba versus desmopressin in treatment of children with monosymptomatic nocturnal enuresis: A randomized controlled trial, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2026.106077

Table 3 Comparison between the studied groups regarding relapse rate and side effects.

	Group 1 (placebo)	Group 2 (GBE)	Group 3 (Desmopressin)	Group 4 (combination therapy)	p-value
Relapse rate	13 (54.2%) [f]	20 (44.4%) [f]	25 (36.8%) [f]	21 (22.2%) [c,d,e]	<0.001[a]
Adverse effect rate	1 (1.1%)	1 (1%)	3 (3%)	3 (2.9%)	0.588
Type of adverse effect					
Headache	0 (0%)	0 (0%)	2 (66.7%)	1 (33.3%)	
Abdominal pain	0 (0%)	0 (0%)	1 (33.3%)	2 (66.7%)	
Sleep disorder	1 (100%)	1 (100%)	0 (0%)	0 (0%)	
Na level[b]					
After 1 week	140.14 ± 3.42	140.0 ± 3.35	140.42 ± 3.23	140.25 ± 3.02	0.822
After 1 month	140.01 ± 3.05	139.98 ± 3.17	139.47 ± 3.41	139.82 ± 3.39	0.642

*, $p < 0.05$ is statistically significant.
[a] $p \leq 0.001$ is statistically highly significant data is represented as number and % and compared using Chi square test.
[b] data is represented as mean ± SD and compared using one way ANOVA test.
[c] significant compared to group 1.
[d] significant compared to group 2.
[e] significant compared to group 3.
[f] significant compared to group 4.

and population differences [30], while combination therapy showed higher response compared to the existing studies mostly since GBE increase sleep arousal and desmopressin act on diuresis showing synergistic effects.

Meta-analyses and randomized controlled trials have reported that Desmopressin offers rapid symptom relief but is associated with higher relapse rates after discontinuation [8,31]. Our study results were comparable with meta-analysis, which assessed the effects of Desmopressin in management of MNE in children combined with alarm therapy or other traditional drugs. Our study evaluated a novel combination of Desmopressin with GBE, which was more effective than Desmopressin alone, and the meta-analysis suggested that combination therapy may be more effective than Desmopressin alone but with low-certainty evidence [30]. Our results demonstrated that this new combination achieved greater reductions in wet nights, higher response rates, lighter sleep, improved arousal and QoL outcomes, and lower relapse rates, highlighting its potential added clinical benefit as substitution for alarm therapy as combination with Desmopressin.

A limitation of our study is the lack of subgroup analyses for children with specific risk factors, such as nocturnal polyuria or sleep arousal disorders, which could affect the response to Desmopressin or GBE. These factors were not separately studied. Nocturnal diuresis volume was not documented as it was not applicable in most cases due to the difficulty of using diapers to weight in children whose mean age is 10 years (refusing to wear ones) Also, long term follow up (beyond 3 months) was not done and short term follow up may limit the detection of safety profile of GBE. Another limitation was the wide age range with lack of age-stratified analysis. Additionally, no documentation was done for the effect on diuresis volume or development of nocturia. One more limitation was that GBE contains different active components. However, there is no consensus which one is responsible for GBE effects, Consequently, no specific active component was used and evaluated separately.

Future studies should involve dose-finding studies to establish the minimal effective nocturnal GBE dose, different GBE components to be evaluated separately and long-term follow-up to assess durability of response and neurocognitive safety, and the development of predictive clinical or investigations to guide the optimal therapy selection across arousal related, urine volume related, and bladder function related MNE.

Conclusion

This randomized, double-blinded, placebo-controlled two centers trial shows that GBE is a safe and effective treatment for children with MNE, either alone or in combination with Desmopressin. While Desmopressin primarily reduces nocturnal urine production, GBE improves the sleep arousal altering sleep quality (transforming it to lighter one) in a manner that does not affect QoL but improving it.

The combination of GBE and Desmopressin makes a significant improvement in wet nights with high full-response rates, lower relapse rates, lighter sleep, better arousal and greater QoL improvement. GBE offers a novel alternative treatment for MNE. Further long-term and dose-related studies are warranted to define the optimal role of GBE in clinical practice and to confirm its neurocognitive safety profile.

Ethics approval statement

The study received ethics approval from our local university ethics committee under the number 11-2024UROL9-4.

Generative AI

Generative AI and AI-assisted technologies were NOT used in the preparation of this work.

Please cite this article as: El-Shazly M et al., Ginkgo biloba versus desmopressin in treatment of children with monosymptomatic nocturnal enuresis: A randomized controlled trial, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2026.106077

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest.

Acknowledgments

The authors would like to express gratitude towards all the patients who participated in our study.

References

[1] Nigri P, Nigri L, Peccarisi L. Overview on the management of nocturnal enuresis in children in general pediatrics. Global Pediatrics 2024;9:100207.
[2] Rangel RA, Seabra CR, Ferrarez C, Soares JL, Choi M, Cotta RG, et al. Quality of life in enuretic children. Int Braz J Urol 2021;47(3):535—41.
[3] Bower WF, Wong EMC, Yeung CK. Development of a validated quality of life tool specific to children with bladder dysfunction. Neurourol Urodyn 2006;25(3):221—7.
[4] EAU. EAU Guidelines on Paediatric Urology — Section 3.12.3.3 Medical treatment. 2025. https://uroweb.org/guidelines/paediatric-urology/chapter/the-guideline.
[5] Ferrara P, Ianniello F, Del Vescovo E, Sodero G, Gatto A, Ruggiero A. Oral desmopressin lyophilisate formulation (MELT): efficacy and safety in children and adults. Biomedical Pharmacology Journal 2018;11(1):171—7.
[6] Nevéus T, Fonseca E, Franco I, Kawauchi A, Kovacevic L, Nieuwhof-Leppink A, et al. Management and treatment of nocturnal enuresis—an updated standardization document from the International Children's Continence Society. J Pediatr Urol 2020;16(1):10—9.
[7] Caldwell PH, Deshpande AV, Von Gontard A. Management of nocturnal enuresis. BMJ 2013;347:f6259.
[8] Purnomo AF, Daryanto B, Nurhadi P. Monosymptomatic nocturnal enuresis treatment using alarm-therapy and desmopressin: a meta-analysis approach. Med Arch 2021;75(6):431—5.
[9] Pedersen MJ, Rittig S, Jennum PJ, Kamperis K. The role of sleep in the pathophysiology of nocturnal enuresis. Sleep Med Rev 2020;49:101228.
[10] Nishimon S, Yamaguchi M, Muraki H, Sakai N, Nishino S. Intraperitoneal injection of ginkgolide B, a major active compound of Ginkgo biloba, dose-dependently increases the amount of wake and decreases non-rapid eye movement sleep in C57BL/6 mice. Neurosci Lett 2020;722:134832.
[11] Shahrajabian MH, Sun W, Cheng Q. Ginkgo biloba: a famous living fossil tree and an ancient herbal traditional Chinese medicine. Curr Nutr Food Sci 2022;18(3):259—64.
[12] Hasanzadeh E, Mohammadi MR, Ghanizadeh A, Rezazadeh SA, Tabrizi M, Rezaei F, et al. A double-blind placebo controlled trial of Ginkgo biloba added to risperidone in patients with autistic disorders. Child Psychiatry Hum Dev 2012;43(5):674—82.
[13] Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn 2016;35(4):471—81.
[14] Uebel-von Sandersleben H, Rothenberger A, Albrecht B, Rothenberger LG, Klement S, NjzfK-uJuP Bock. Ginkgo biloba extract EGb 761® in children with ADHD. 2014.
[15] Ong LM, Chan JMF, Koh GEMY, Gopal PE-W, Leow EHM, Ng YH. Approach to nocturnal enuresis in children. Singapore Medical Journal 2024;65(4):242—8.
[16] Hjalmas K, Arnold T, Bower W, Caione P, Chiozza LM, von Gontard A, et al. Nocturnal enuresis: an international evidence based management strategy. J Urol 2004;171(6 Pt 2):2545—61.
[17] Neveus T, Eggert P, Evans J, Macedo A, Rittig S, Tekgul S, et al. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol 2010;183(2):441—7.
[18] Maternik M, Krzeminska K, Zurowska A. The management of childhood urinary incontinence. Pediatr Nephrol 2015;30(1):41—50.
[19] Montaldo P, Tafuro L, Rea M, Narciso V, Iossa AC, Del Gado R. Desmopressin and oxybutynin in monosymptomatic nocturnal enuresis: a randomized, double-blind, placebo-controlled trial and an assessment of predictive factors. BJU Int 2012;110(8 Pt B):E381—6.
[20] Balk EM, Adam GP, Corsi K, Mogul A, Trikalinos TA, Jeppson PC. Adverse events associated with nonsurgical treatments for urinary incontinence in women: a systematic review. J Gen Intern Med 2019;34(8):1615—25.
[21] Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. BMC Geriatr 2015;15(1):31.
[22] Welk B, Richardson K, Panicker JN. The cognitive effect of anticholinergics for patients with overactive bladder. Nat Rev Urol 2021;18(11):686—700.
[23] Chatterjee S, Kondratskaya E, Krishtal O. Structure-activity studies with Ginkgo biloba extract constituents as receptor-gated chloride channel blockers and modulators. Pharmacopsychiatry 2003;36(S 1):68—77.
[24] Ivic L, Sands TT, Fishkin N, Nakanishi K, Kriegstein AR, Stromgaard K. Terpene trilactones from Ginkgo biloba are antagonists of cortical glycine and GABA(A) receptors. J Biol Chem 2003;278(49):49279—85.
[25] Ghadim MBA, Salimi-Sabour E, Shahriari A, Niazi M, Bahrami F. Evaluating ginkgetin from Ginkgo biloba as a novel agent for sleep promotion through molecular docking and in vivo studies. Iran J Basic Med Sci 2025;28(6):746.
[26] Niederhofer H. Ginkgo biloba treating patients with attention-deficit disorder. Phytother Res 2010;24(1):26—7.
[27] Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. Ginkgo for memory enhancement: a randomized controlled trial. JAMA 2002;288(7):835—40.
[28] Kamperis K, Hagstroem S, Rittig S, Djurhuus JC. Combination of the enuresis alarm and desmopressin: second line treatment for nocturnal enuresis. J Urol 2008;179(3):1128—31.
[29] Song P, Huang C, Wang Y, Wang Q, Zhu W, Yue Y, et al. Comparison of desmopressin, alarm, desmopressin plus alarm, and desmopressin plus anticholinergic agents in the management of paediatric monosymptomatic nocturnal enuresis: a network meta-analysis. BJU Int 2019;123(3):388—400.
[30] Hahn D, Stewart F, Raman G. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev 2025;7(7):CD002112.
[31] Zhai R, Shao S, Lv L, Li S, Wang Y, Zhang Y, et al. Efficacy of desmopressin and enuresis alarm in the treatment of monosymptomatic nocturnal enuresis: a multicenter prospective randomized controlled study. Pediatr Nephrol 2025;40(10):3137—44.

Please cite this article as: El-Shazly M et al., Ginkgo biloba versus desmopressin in treatment of children with monosymptomatic nocturnal enuresis: A randomized controlled trial. Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2026.106077