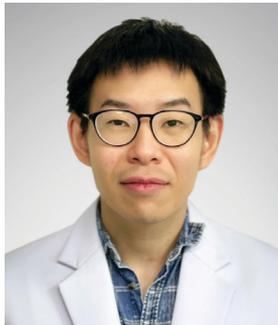


# Nocturnal Enuresis: A Review and Focus on The Treatment Modalities of Monosymptomatic Nocturnal Enuresis

Prakasit Wannapaschaiyong, MD<sup>1</sup> ; Sitthiphon Bunman, PhD<sup>2</sup>



Prakasit Wannapaschaiyong, MD

## Abstract

Nocturnal enuresis is a common problem in children. It has significant psychological impacts on both children and families. Nocturnal enuresis refers to an inability to hold urine during sleep at night. The cause of nocturnal enuresis may result from several related factors. The evaluation requires a thorough history, a complete physical examination, a voiding diary, and an appropriate investigation. Treatment can be tailored according to the patient's underlying cause. In the present study, the author aimed to assemble etiologies, diagnosis evaluation, modalities of treatment, and general information about nocturnal enuresis.

**Keywords :** Nocturnal enuresis, monosymptomatic, pathogenesis, treatment

Nocturnal Enuresis (Bedwetting) significantly impacts children and families, especially emotional well-being, self-esteem, interpersonal relationships, and socialization.<sup>1,2</sup> However, both domestic and international studies have found only a minority of caregivers have brought this problem to consult a physician.<sup>3</sup> Therefore, physicians play a key role in finding the problem to provide advice and help children receive appropriate treatment at an early stage, resulting in a better quality of life for children and families.<sup>4</sup>

## Definitions

The definition of enuresis in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) refers to repeated voiding of urine into bed or clothes, occurring at least twice a week for at least 3 consecutive months in children older than 5 years of age (or the developmental equivalent). Enuresis is divided into nocturnal enuresis (wetting while asleep at night) and diurnal enuresis (daytime wetting while awake).<sup>5</sup>

The International Children's Continence Society (ICCS),<sup>6</sup> however, uses the term intermittent urinary incontinence, which refers to involuntary wetting, and classifies it into two categories. First, enuresis, also known as nocturnal enuresis, is defined as nighttime wetting at least once a week for at least 3 consecutive months in a child 5 years of age or older. Another is daytime urinary incontinence, which includes daytime wetting at least once every 2 weeks. Furthermore, enuresis is classified as monosymptomatic (MNE) or non-monosymptomatic (NMNE), with the latter correlating with lower urinary tract symptoms such as severe frequency, urgency, urine leaking, abnormalities of urine stream, or daytime incontinence.<sup>7</sup>

In addition, enuresis can be categorized into primary and secondary forms. Primary enuresis is defined as the child who has never obtained continence, whereas secondary enuresis is the one that has been continent for at least 6 months and become incontinent.<sup>5</sup>

<sup>1</sup> Department of Pediatrics, Taksin Hospital, Bangkok, Thailand.

<sup>2</sup> Faculty of Medicine, Thammasat University, Pathumthani, Thailand.

\* Address Correspondence to author:  
Prakasit Wannapaschaiyong, MD  
Department of Pediatrics,  
Taksin Hospital  
543 Somdet Chao Phraya Road,  
Khlong San Subdistrict, Khlong San District,  
Bangkok 10600, Thailand  
email: pra\_ka\_sit@hotmail.com

## Epidemiology

The prevalence of nocturnal enuresis among school-age children in Thailand is 3.9%<sup>3</sup>, while international studies have found that the prevalence varies from 8-21%.<sup>8-14</sup> This difference in prevalence data may result from diverse diagnostic criteria since Thailand uses the DSM-5 while other countries use the ICCS.

## Pathogenesis

MNE is caused by one or a combination of several factors which include:

### 1. Genetics

Genetic predisposition to enuresis studies show a 44% chance of enuresis in children with one affected parent and 77% in those with two affected parents.<sup>15</sup> Identical twins have the highest concordance rate (68%).<sup>16</sup> However, we are currently unable to identify the specific gene.

### 2. Nocturnal polyuria

Approximately 50-70% of enuretic children have a large volume of relatively diluted urine during sleep compared to age-matched peers.<sup>9,17</sup> The cause of nocturnal polyuria may be associated with vasopressin deficiency or alterations in its circadian release. In addition, there may be a small subgroup of enuretic children with impaired renal sensitivity to vasopressin.<sup>18</sup>

### 3. Small bladder capacity

Bladder capacity tends to be decreased in children with enuresis compared with age-matched children without enuresis. The reduced bladder capacity appears to be functional rather than anatomic. The reflects differences in function bladder capacity with contractions occurring earlier in filling.<sup>19</sup>

### 4. Detrusor overactivity

32% of children with nocturnal enuresis had involuntary detrusor contractions that resulted in enuresis.<sup>20</sup> This can be related to increased bladder irritability, usually due to a urinary tract infection and constipation.<sup>21,22</sup>

### 5. High arousal threshold

Children with nocturnal enuresis usually sleep deeply. Neveaus reviewed by questionnaire 1,413 children between the ages of six and ten and noted that enuresis was associated with subjectively high threshold arousal and significant confusion upon awakening from sleep. Many children exposed to alarm therapy sleep through the alarm while family members awaken.<sup>23</sup> Obstructive sleep apnea (OSA) can be associated with nocturnal enuresis.<sup>24</sup> Some researchers suggest that chronic over-stimulation in the child with OSA leads to downregulation of the voiding center, which precedes to decrease in the child's sense of full bladder and subsequent bedwetting.<sup>25</sup>

### 6. Maturation delay

The delayed maturation of the normal developmental process results in the enuretic child's inability to send, perceive or respond to information about a filled bladder during the night. From the literature review, children with enuresis usually have a higher prevalence of motor clumsiness, perceptual dysfunction, and speech disturbances. That evidence supports the correlation theory between maturation delay and enuresis.<sup>26-29</sup>

### 7. Stress or Psychological problems

Children's stress, such as having a new sibling, parental divorce, relocation, separation from a loved one, and severe psychological conditions, especially sexual abuse, may exacerbate or contribute to enuresis.<sup>9</sup>

NMNE, on the other hand, is usually caused by neurogenic bladder and urinary tract malformation.<sup>19</sup> Furthermore, other conditions, such as diabetes mellitus, diabetes insipidus, urinary tract infection, epilepsy, and chronic kidney disease, may be present with bedwetting.<sup>19</sup>

## Diagnosis

A complete history should be obtained focused on questions to differentiate between MNE and NMNE, as further investigation of organic pathology is needed in children with NMNE. Moreover, the history of distinguishing between primary and secondary enuresis is also vital because secondary enuresis is often associated with stress and psychological problems.<sup>30,31</sup>

Physical examination should be performed, emphasizing the spinal, neurologic, and genital examinations to exclude other diseases that cause urinary incontinence, such as spinal cord abnormalities and genitourinary tract abnormalities (e.g., ectopic ureter, partial labial fusion). Examination for constipation is also crucial because constipation is frequently related to wetting.<sup>17,19</sup>

A voiding diary is a record of fluid intake and urine output that can help physicians differentiate between causes of nocturnal enuresis. Caregivers are encouraged to complete data for 2 consecutive days.<sup>17,19,32</sup> Each daytime and last urine output before bedtime, excluding first-morning void, are noted to calculate bladder capacity. If the maximum voided volume is less than 65% of expected bladder capacity (EBC), small bladder capacity may be the cause of nocturnal enuresis.<sup>6</sup> The sum of total nocturnal urine output and first-morning void, excluding last urination before bedtime, is recorded to assess nocturnal urine. If nocturnal urine is more significant than 130% of EBC, the cause of nocturnal enuresis may be nocturnal polyuria.<sup>6</sup> EBC can be calculated from the Koff formula ( $bladder\ capacity = (age\ in\ year + 2) \times 30$ ), which is used for children 4-12 years old, and the result of this formula is in milliliters.<sup>33</sup>

The laboratory evaluation besides a urinalysis is usually unnecessary since this test will show a low specific gravity in diabetes insipidus, glycosuria in case of diabetes mellitus, and the presence of nitrites leukocyte esterase, leukocytes, or bacteria in case of infection.<sup>19</sup> There is no indication for the use of imaging techniques or urodynamic studies except in cases that patients are NMNE or do not respond to initial treatment.<sup>17,19</sup>

## Treatment

The primary goals in the treatment of nocturnal enuresis are to alleviate the problem and reduce its psychological impact on the child and family. Initial intervention should be **helping children and families to understand this condition**. They should be told that bedwetting is a common condition and can be caused by a variety of reasons, but it is not the child's intention and not the child's fault.<sup>15,17</sup> When a child has NMNE, the organic cause should be identified and treated appropriately. However, MNE does not usually have an apparent organic cause. Therefore, in this review, the author emphasizes the treatment of MNE, which are as follows:

**1. Behavioral modification**, such as limiting fluids in the evening,<sup>17,32</sup> avoiding beverages and foods with caffeine, and encouraging voiding before bedtime,<sup>15,34</sup> is the first step treatment in MNE. If the child with MNE has constipation or OSA, these conditions should be treated to increase the efficacy of enuretic treatment.<sup>15,17</sup>

**2. Motivational therapy**, for example praising or rewarding a child for decreasing nighttime fluid intake and pre-bedtime voids, can be effective in up to a quarter of children aged 5-7 years who are already showing signs of multiple dry nights a week.<sup>34</sup> In one positive reinforcement system, the child puts stickers on a chart or earns points for every night he or she remains dry. Once a certain number of stickers or points have been earned, the child is given a prize.<sup>35</sup>

The child with MNE should begin the treatments as mentioned above and follow up for 3-6 months. If the result is rarely effective, additional therapeutic modalities should be started, such as alarms and medication.<sup>17,31,34</sup>

**3. The enuretic alarm** is believed to work through a classically conditioned response.<sup>17</sup> A device with a moisture sensor is attached to the child's underpants and is connected to the alarm. When a child urinates in his underwear, it can cause an auditory or vibration alarm to wake the child up and continue urinating in the bathroom. The child will establish a link between the alarm and a full bladder. By learning the behavior of going to the bathroom, the child will wake up and go to the bathroom himself when the bladder is full.<sup>17,34</sup> This treatment works best in older children motivated to achieve dryness.<sup>32</sup> Alarm therapy has reported success rates of 30-60%,<sup>15</sup> with a treatment duration of 2-3 months and stated relapse rates of 50%.<sup>17</sup> If this therapy is applied

continuously for 4-5 months, it can reduce the recurrence rate. Despite the recurrence of the symptoms, Alarm therapy can be reused, which is shown to be effective.<sup>17,34</sup>

Alarm therapy requires a caregiver's involvement because the caregiver who hears the alarm must wake the child if the child does not wake up on their own. Therefore, this treatment is not suitable for families with a poor parent-child relationship.<sup>35</sup>

**4. Pharmacological therapy** is considered in case of failure to improve with behavioral modification and alarm therapy or if the clinical scenario suggests specific underlying pathophysiology that can be treated with targeted medication therapy.<sup>17,34</sup> Pharmacologic treatment is not recommended for children under six years of age.<sup>15</sup> Medications are as follows:

**4.1 Desmopressin** is a synthetic analog of vasopressin, which works by decreasing urine production at night, and thus desmopressin has shown to be effective in treating nocturnal polyuria.<sup>32</sup> It is also helpful for sleepovers or overnight camps.<sup>17</sup> The oral form of desmopressin is only recommended because the intranasal form is associated with an increased risk of hyponatremic seizures.<sup>15,34</sup> The initial dose of regular tablets is 0.2 mg, and it can be incremented to 0.4 mg after 10-14 days for achieving the best effect. Treatment should be discontinued after 3 months to see if enuresis has resolved. Desmopressin is administered orally 60 minutes before bedtime. The anti-enuretic effect is immediate.<sup>34</sup> There are concerns about hyponatremia from water intoxication while taking desmopressin, so fluid intake should be limited to 8 ounces from one hour before to eight hours after administration.<sup>17,34,35</sup> Desmopressin is up to 40% effective in treating nocturnal enuresis,<sup>15</sup> but the rate of recurrence after discontinuation is as high as 60-70%.<sup>34</sup>

**4.2 Anticholinergic agents** (i.e., oxybutynin and tolterodine) are the current gold standard in treating patients with detrusor overactivity or small bladder capacity. These agents act by reducing the frequency and intensity of uninhibited detrusor contractions during the bladder's filling phase, thereby increasing the functional bladder capacity and compliance. Constipation is an adverse effect of this group of medications, which may lead to ineffective treatment of enuresis, so the side effect should be monitored.<sup>15,17</sup>

**4.3 Tricyclic antidepressants** (i.e., imipramine) are another pharmacological option that should be reserved for non-responders to desmopressin and anticholinergic agents. Its mechanism of action has been proposed to involve stimulating vasopressin secretion and relaxation of the detrusor muscle. Its response rate is 30-60%, but the recurrence rate is very high after discontinuation. Adverse effects of tricyclic antidepressants are relatively uncommon but may be severe. Side effects of this group include cardiac arrhythmia, liver toxicity, and central nervous system depression.<sup>15,17,34</sup>

### 5. Combining desmopressin and the enuretic alarm

has been recommended to treat refractory nocturnal enuresis. This approach can lead to a higher response rate.<sup>15,17,32</sup>

### Prognosis

The spontaneous remission rate for primary MNE is 15% per year.<sup>36</sup> However, the condition is associated with a negative impact on child's and family quality of life, leads to low self-esteem, emotional problems, and high levels of stress.<sup>1,2,37</sup> Effective treatment of enuresis can improve the quality of life of patients.<sup>37</sup>

### References

- Jönson Ring I, Nevéus T, Markström A, et al. Nocturnal enuresis impaired children's quality of life and friendships. *Acta Paediatr* 2017;106(5):806-11.
- Collis D, Kennedy-Behr A, Kearney L. The impact of bowel and bladder problems on children's quality of life and their parents: A scoping review. *Child Care Health Dev* 2019;45(1):1-14.
- Hansakunachai T, Ruangdaraganon N, Udomsubpayakul U, et al. Epidemiology of enuresis among school-age children in Thailand. *J Dev Behav Pediatr* 2005;26(5):356-60.
- Perez J. Early intervention for childhood continence problems. *Community Pract* 2014;87(7):44-6.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5<sup>th</sup> ed. American Psychiatric Association DSMTF, editors. Arlington, VA: American Psychiatric Association; 2013.
- Austin PF, Bauer SB, Bower W, 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.
- Thurber S. Childhood Enuresis: Current Diagnostic Formulations, Salient Findings, and Effective Treatment Modalities. *Arch Psychiatr Nurs* 2017;31(3):319-23.
- Sarici H, Telli O, Ozgur BC, et al. Prevalence of nocturnal enuresis and its influence on quality of life in school-aged children. *J Pediatr Urol* 2016;12(3):159 e1-6.
- Neveus T. Pathogenesis of enuresis: Towards a new understanding. *Int J Urol* 2017;24(3):174-82.
- Kanaheswari Y. Epidemiology of childhood nocturnal enuresis in Malaysia. *J Paediatr Child Health* 2003;39(2):118-23.
- Yousef KA, Basaleem HO, bin Yahiya MT. Epidemiology of nocturnal enuresis in basic schoolchildren in Aden Governorate, Yemen. *Saudi J Kidney Dis Transpl* 2011;22(1):167-73.
- Hashem M, Morteza A, Mohammad K, et al. Prevalence of nocturnal enuresis in school aged children: the role of personal and parents related socio-economic and educational factors. *Iran J Pediatr* 2013;23(1):59-64.
- Bakhtiar K, Pournia Y, Ebrahimzadeh F, et al. Prevalence of nocturnal enuresis and its associated factors in primary school and preschool children of khorramabad in 2013. *Int J Pediatr* 2014;2014:120686.
- Eneh CI, Okafor HU, Ikefuna AN, et al. Nocturnal enuresis: prevalence and risk factors among school-aged children with sickle-cell anaemia in a South-east Nigerian city. *Ital J Pediatr* 2015;41:66.
- Walker RA. Nocturnal Enuresis. *Prim Care* 2019;46(2):243-248.
- Hublin C, Kaprio J, Partinen M, et al. Nocturnal enuresis in a nationwide twin cohort. *Sleep* 1998;21(6):579-85.
- Caldwell P, Deshpande A. Nocturnal enuresis resource kit 2<sup>nd</sup> edition-a tool for healthcare professionals: The Children's Hospital at Westmead and John Hunter Children's Hospital 2018. (Accessed January 16, 2022, <https://www.neresourcekit.com.au/Nocturnal%20Enuresis%20Resource%20Kit%20second%20edition.pdf>).
- Kim JM, Park JW, Lee CS. Evaluation of nocturnal bladder capacity and nocturnal urine volume in nocturnal enuresis. *J Pediatr Urol* 2014;10(3):559-63.
- Tu ND, Baskin LS, Amhym AM. Nocturnal enuresis in children: etiology and evaluation 2021. (Accessed January 16, 2022, [https://www.uptodate.com/contents/nocturnal-enuresis-in-children-etiology-and-evaluation?sectionName=EPIDEMIOLOGY%20AND%20NATURAL%20HISTORY&topicRef=2863&anchor=H2&source=see\\_link#H1](https://www.uptodate.com/contents/nocturnal-enuresis-in-children-etiology-and-evaluation?sectionName=EPIDEMIOLOGY%20AND%20NATURAL%20HISTORY&topicRef=2863&anchor=H2&source=see_link#H1)).
- Watanabe H. Sleep patterns in children with nocturnal enuresis. *Scand J Urol Nephrol Suppl* 1995;173:55-6;discussion 56-7.
- Veiga ML, Lordelo P, Farias T, et al. Constipation in children with isolated overactive bladders. *J Pediatr Urol* 2013;9:945-9.
- Wallace KM, Drake MJ. Overactive bladder. *F1000Res* 2015;4:F1000 Faculty Rev-1406.
- Neveus T, Hetta J, Cnattingius S, et al. Depth of sleep and sleep habits among enuretic and incontinent children. *Acta Paediatr* 1999;88(7):748-52.
- Veeravigrom M, Desudchit T. Prevalence of Sleep Disorders in Thai Children. *Indian J Pediatr* 2016;83(11):1237-41.
- Su MS, Xu L, Pan WF, et al. Current perspectives on the correlation of nocturnal enuresis with obstructive sleep apnea in children. *World J Pediatr* 2019;15(2):109-16.
- Jarvelin MR. Developmental history and neurological findings in enuretic children. *Dev Med Child Neurol* 1989;31(6):728-36.

### Conclusion

The identifying of the type of nocturnal enuresis is essential since it affects the selection of investigation and treatments. Management of MNE should begin with effective behavioral modification and motivational therapy. Additional treatment must take into consideration the possible pathophysiological mechanisms. Alarm treatment is an effective treatment modality for older children motivated to achieve dryness. Desmopressin is mainly used in the treatment of MNE, caused by nocturnal polyuria, while combined therapy is a treatment of choice in case of failure to improve with a single treatment modality.

27. Jarvelin MR, Moilanen I, Kangas P, et al. Aetiological and precipitating factors for childhood enuresis. *Acta Paediatr Scand* 1991;80(3):361-9.
28. von Gontard A, Freitag CM, Seifen S, et al. Neuromotor development in nocturnal enuresis. *Dev Med Child Neurol* 2006;48(9):744-50.
29. Buckley BS, Lapitan MC. Epidemiology Committee of the Fourth International Consultation on Incontinence. Prevalence of urinary incontinence in men, women, and children current evidence: findings of the Fourth International Consultation on Incontinence. *Urology* 2010;76(2):265-70.
30. Bogaert G, Stein R, Undre S, et al. Practical recommendations of the EAU-ESPU guidelines committee for monosymptomatic enuresis-Bedwetting. *Neurourol Urodyn* 2020;39(2):489-97.
31. Centre NCG. Bedwetting in children and young people overview. London 2020. (Accessed January 16, 2022, <https://pathways.nice.org.uk/pathways/bedwetting-in-children-and-young-people>).
32. Vande Walle J, Rittig S, Tekgul S, et al. Enuresis: practical guidelines for primary care. *Br J Gen Pract* 2017;67(660):328-9.
33. Kang BJ, Chung JM, Lee SD. Evaluation of functional bladder capacity in children with nocturnal enuresis according to type and treatment outcome. *Res Rep Urol* 2020;12:383-9.
34. Tu ND, Baskin LS. Nocturnal enuresis in children: management 2020. (Accessed January 16, 2022, <https://www.uptodate.com/contents/nocturnal-enuresis-in-children-management>).
35. O'Flynn N. Nocturnal enuresis in children and young people: NICE clinical guideline. *Br J Gen Pract* 2011;61(586):360-2.
36. Graham KM, Levy JB. Enuresis. *Pediatr Rev* 2009;30(5):165-72.
37. Van Herzeele C, De Bruyne P, De Bruyne E, et al. Challenging factors for enuresis treatment: Psychological problems and non-adherence. *J Pediatr Urol* 2015;11(6):308-13.