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Management of nocturnal enuresis

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Nocturnal enuresis (enuresis or bedwetting) is the most common type of urinary incontinence in children. Depending on the definition, prevalence is 8-20% for 5 year olds, 1.5-10% for 10 year olds, and 0.5-2% for adults, with 2.6% of 7.5 year old children wetting on two or more nights a week.¹ Prevalence seems to be similar worldwide. Here, we review current knowledge about the treatment of this common condition.

What is nocturnal enuresis?

Nocturnal enuresis is intermittent involuntary voiding during sleep in the absence of physical disease in a child aged 5 years or more. A minimum of one episode a month for at least three months is required for the diagnosis to be made.²

Who gets nocturnal enuresis?

A large epidemiological study showed that nocturnal enuresis is more common in males at all ages, and is more likely to persist in those with frequent wetting.³ Nocturnal enuresis is usually idiopathic and is commonly associated with daytime urinary incontinence (seen in 3.3% of 7.5 year olds in a large epidemiological study¹), faecal incontinence, and chronic constipation. In a tertiary continence service, 36% of children with nocturnal enuresis reported constipation,⁴ and enuresis resolves in about two thirds of such children when constipation is treated.⁵ About 30% of children with sleep disordered breathing have nocturnal enuresis, probably because of impaired sleep quality, and enuresis resolves in half of these children after corrective surgery.⁶ Similarly, about 30% of obese children have nocturnal enuresis,⁷ which is more resistant to treatment.⁸

Nocturnal enuresis is more common in children with developmental delay, physical or intellectual disabilities, and psychological or behavioural disorders. It occurs in 20-40% of children with psychological or behavioural disorders, such as attention-deficit/hyperactivity disorder (ADHD) (the most common), autism spectrum disorder, anxiety, and depressive or conduct disorders.² In these children, enuresis is more likely to be persistent, possibly because of lower adherence to treatment.

According to a US survey,⁹ many parents attribute an emotional cause to nocturnal enuresis. Although comorbid psychological disorders are more common in these children

SOURCES AND SELECTION CRITERIA

We searched Medline, Embase, and the *Cochrane Database of Systematic Reviews* using the search terms "enuresis" or "bedwetting" as keywords. Systematic reviews, meta-analyses, population based studies, randomised controlled trials, and studies published in the past five years were prioritised.

(20-40% compared with 10% of continent children),¹⁰ and can interact with underlying genetic and environmental factors (such as diet, fluid consumption, toileting habits, and urinary tract infections), they are not the main cause of nocturnal enuresis.

What is the underlying pathophysiology of nocturnal enuresis?

A history of nocturnal enuresis in a parent or relative is found in 20-40% and 60-70% of affected children, respectively.¹¹ Advances in neuroimaging led by functional magnetic resonance imaging have shown that children with enuresis have microstructural abnormalities and delay in the maturation of the neuronal circuits in the prefrontal cortex. These findings support the theory of delayed maturation as a cause for nocturnal enuresis.^{12,13}

Nocturnal enuresis results from the interplay of three physiological factors: defective sleep arousal; nocturnal polyuria; and bladder factors, such as lack of inhibition of bladder emptying during sleep, reduced bladder capacity, or bladder overactivity (box).¹⁴

The child's bladder capacity can be determined by comparing the maximum voided volume (largest void during the day) with the expected bladder capacity. An acceptable range is 65-150% of expected bladder capacity. If the maximum voided volume is noticeably smaller than the expected bladder capacity, it may indicate poor fluid intake, constipation, or overactive bladder syndrome (non-monosymptomatic nocturnal enuresis). According to a case-control study, children with a small or overactive bladder wet during sleep when urine volume exceeds bladder capacity or as a result of detrusor overactivity.¹⁹ Usually, these children will also show daytime bladder symptoms, although this is not always the case.²⁰

A case-control study comparing children with severe refractory nocturnal enuresis with controls found significantly more cortical arousal (without complete awakening) during sleep in those with enuresis, which correlated with unprovoked bladder contractions. It is therefore thought that these children may have chronic overstimulation of the arousal centre, which may cause a paradoxical suppression and an inability to arouse to bladder signals.²¹

How do you assess nocturnal enuresis?

The International Children's Continence Society (ICCS) classifies nocturnal enuresis according to when it started

SUMMARY POINTS

Nocturnal enuresis can be associated with daytime urinary incontinence, bowel problems, developmental or psychological problems, and sleep disordered breathing. Nocturnal enuresis commonly results from defective sleep arousal, nocturnal polyuria, lack of inhibition of bladder emptying during sleep, and reduced bladder capacity.

Nocturnal enuresis affects quality of life and self esteem, which improve with successful treatment.

The condition responds well to enuresis alarm training or desmopressin. In non-monosymptomatic nocturnal enuresis, treat daytime lower urinary tract symptoms first. In treatment resistance, a repeat thorough assessment and combination therapy may be effective.

(primary or secondary) and whether lower urinary tract symptoms are present (non-monosymptomatic or monosymptomatic).² Clinical, therapeutic, and pathogenic differences between these subtypes influence treatment choice.

Obtaining an accurate history is crucial for assessment and is recommended by the ICCS report and the National Institute for Health and Care Excellence (NICE) guideline, which are based on reviews of the literature.^{2–22} The aim of this thorough assessment is to establish the diagnosis, identify or exclude underlying causes, identify factors that may influence the choice of management strategy, and understand what the family wants.²²

In primary care, a detailed history of the wetting, toileting patterns, fluid intake, comorbidities, and the family's situation, as well as a thorough examination to assess for constipation and neurogenic and urological causes, are recommended. A bladder diary documenting daytime fluid intake and urine output over 48 hours and incontinence episodes over seven days should also be obtained, and a screening questionnaire for behavioural symptoms undertaken. Urine analysis to exclude diabetes, kidney disease, and urinary tract infections; renal ultrasound to identify underlying urological disease in those with non-monosymptomatic enuresis; and uroflowmetry to assess bladder function can be useful but are non-essential,^{2–22} because of a lack of evidence to support their non-selective use.

Rarely, structural anomalies of the urinary tract, such as posterior urethral valves and neurogenic lower urinary tract dysfunction, can present with enuresis. Continuous (daytime and night time) urinary incontinence may be the presenting symptom in children with ectopic ureters, complex ureteroceles, and other severe malformations of the lower urinary tract, such as extrophy of the bladder. Abnormal urinary tract ultrasound scans and a history of urological interventions should alert the clinician to an underlying urological cause.

Most affected children have primary enuresis and have never attained night time continence. Those with secondary enuresis start bedwetting after attaining night dryness for at least six months. Primary and secondary enuresis are similar in presentation,²³ although secondary enuresis is thought to be more often associated with pathological or psychological causes, including behavioural or emotional disorders, stressful life events, and constipation. The NICE guideline recommends asking about specific triggers in secondary enuresis and advises considering child maltreatment if secondary enuresis (or daytime wetting) persists despite adequate assessment and management.²²

Those with non-monosymptomatic nocturnal enuresis also have lower urinary tract symptoms in the daytime, such as urgency, frequency, abnormal urine stream, or holding manoeuvres, which indicate an associated lower urinary tract dysfunction, such as overactive bladder, underactive bladder, or dysfunctional voiding. They are more treatment resistant according to a large cohort study,²⁴ and treatment of nocturnal enuresis should begin by dealing with any underlying daytime bladder problems. If enuresis persists once these are resolved, it can be treated by alarm training or desmopressin.²⁵

Physiological factors involved in nocturnal enuresis

Defective sleep arousal

In most children with enuresis the arousal response is defective during sleep. When urine volume exceeds bladder capacity, bedwetting occurs.¹⁵ Although arousability is reduced, the sleep architecture itself is usually unaltered, and enuresis occurs in all sleep stages, particularly during non-REM (rapid eye movement) sleep.¹⁶

Nocturnal polyuria

According to case-control studies, many children with nocturnal enuresis have an altered diurnal rhythm of vasopressin secretion,¹⁷ resulting in the production of excessive amounts of relatively dilute urine overnight. The expected bladder capacity is calculated by the formula: (age in years + 1) × 30 mL, which is valid from 2 to 12 years. Nocturnal polyuria is defined as greater than 130% of the expected bladder capacity for age.

Bladder factors

In children with nocturnal enuresis, the emptying reflexes of the full bladder are not adequately inhibited during sleep, resulting in involuntary voiding.¹⁸ The pontine micturition centre of the brain stem is involved in this process.

How does nocturnal enuresis affect the child and family?

Nocturnal enuresis is socially stigmatising and can affect quality of life and psychosocial wellbeing. Children report lower self esteem, which improves with successful treatment.²⁶ In a large population based study, 36.7% of 9 year olds who were dry and 45.6% of children with enuresis ranked nocturnal enuresis as the eighth most stressful life event after items such as not having friends and being teased.²⁷ Their impaired health related quality of life is comparable to chronic conditions such as asthma and diabetes. Surprisingly, a child's perceived quality of life seems to be unrelated to the severity of enuresis but is associated with non-modifiable factors such as age, sex, and ethnicity,²⁸ with poorer quality for older children and those from culturally and linguistically diverse populations.

Nocturnal enuresis can limit social opportunities, such as school camps and sleepovers, and it affects relationships with peers. Although 84% of children in a cohort study reported no problems with teasing, 48% indicated that their friends were aware of their enuresis, which caused them embarrassment.²⁹ Nocturnal enuresis presents a financial burden for families, with increased costs for laundry, disposables, and medical care. Although most parents in a US study reported not getting angry with their child for bedwetting,²⁹ studies from Turkey³⁰ and Brazil³¹ reported that punishment was common and domestic violence sometimes occurred.

When should nocturnal enuresis be treated?

Most children are unhappy about this problem, although 14% were not willing to do anything to become dry, according to a cohort study of 100 patients.²⁹ Health seeking behaviour varies from country to country, with most not seeking medical advice. In a UK study of 8269 children, 31.9% (68/213) of parents reported they had consulted a health worker, 19.2% (41/213) had used an alarm, and 13.1% (28/213) had received medication for their child.³² Similarly in Australia, a third of families

seek medical advice.³³ In Africa, few seek medical advice (2% in the Democratic Republic of Congo, none in south west Nigeria) because of the lack of free medical services and lack of concern about bedwetting.^{34 35}

Medical treatment is recommended from 5 years of age, when nocturnal enuresis is defined as a disorder, particularly if the child and family are motivated to engage in treatment. In younger children, simple measures such as ensuring adequate fluid intake, appropriate toileting behaviour, managing constipation, and a trial of removal of nappies can be attempted.

When should I refer?

Further assess or refer children with nocturnal enuresis if they have severe daytime symptoms, a history of recurrent urinary tract infections, abnormal renal ultrasound results, known or suspected physical or neurological problems, comorbid conditions (such as faecal incontinence; diabetes; and attention, learning, behavioural, or emotional problems), or family problems.²² Also refer those who have not responded to treatment after six months.

What are the treatment options?

Choice of treatment depends on the frequency and severity of the enuresis, the child's age and motivation, the parent or carer's ability to cope, supportive treatment, and whether short term dryness is a priority.

Conservative measures

Conservative non-surgical, non-pharmacological treatment for lower urinary tract dysfunction (also known as urotherapy) is encouraged for all children. This includes providing support and education about the condition and advice about voiding and avoiding caffeine based drinks, encouraging adequate fluid intake (fluid restriction can worsen bladder function), and managing constipation. Correct voiding posture is for the child to undress adequately and sit securely on the toilet, with buttock and foot support, in a comfortable hip abduction position for girls.³⁶ A comfortable posture will help relax the pelvic floor muscles, and shaking or gently squeezing of the penis may be necessary in boys to expel excess urine trapped in the foreskin or on the glans. Children should void every two to three hours during the day and avoid holding on when they feel the urge to urinate. The NICE guideline recommends conservative measures,²² although evidence of their efficacy is limited. In our experience, conservative measures alone can sometimes be effective.

Simple behavioural therapies

Families often try simple behavioural therapies—such as fluid restriction, rewards, and taking the child to the toilet at night—as first attempts to manage the problem.³⁷ A small randomised controlled trial found that more children became dry when rewarded (relative risk 0.84, 95% confidence interval 0.73 to 0.95),³⁸ when lifted during the night (0.79, 0.68 to 0.92),³⁹ or both (0.22, 0.06 to 0.78).⁴⁰ Avoid ineffective and even potentially harmful strategies, such as fluid restriction, retention control training (encouraging the child not to void for as long as possible to expand bladder capacity), and unnecessary drugs. Rewarding

agreed behaviour (such as drinking adequately, voiding before sleep, and engaging in management) may be more effective than rewarding dry nights, which are out of the child's conscious control.²² Although simple behavioural therapies are superior to no active treatment, they are inferior to confirmed effective treatments.³⁷

Alarm training

Alarm training is a first line treatment for nocturnal enuresis and is the most effective long term one, as shown in a systematic review of 56 trials in children.⁴¹ Alarms have been used since 1938 and represent operant behavioural techniques. The response is more gradual and sustained than for drugs, with about two thirds of children becoming dry during treatment and nearly half remaining dry after treatment completion.⁴¹ Alarms train children to suppress bladder emptying during sleep or to wake to void by signalling when they urinate. Bell and pad alarms are placed on the bed, whereas personal alarms are worn in the child's underwear. Both types are equally effective.⁴²

The NICE guideline and the ICCS recommend continuing alarm training for a maximum of 16 weeks or until 14 consecutive dry nights are achieved.^{2 22} Children who do not continue to improve after six weeks of alarm training are unlikely to become completely dry with this technique.⁴³ Alarm training, although effective, can be onerous for families, and the disruption to sleep can cause stress for the child and family. Contraindications to alarm training include lack of motivation by the child and family, crowded housing, family stress, and intolerance to sleep disturbance (because of high parental job demands, breastfeeding infants, or illness in the family).

Alarm training can be reinforced with additional behavioural therapy components. For example, in "overlearning" additional fluids are given at bedtime while alarm training is continued after dryness has been achieved.⁴⁴ When alarm training without overlearning, the child trains to inhibit urination without necessarily learning to wake to void. A systematic review (relative risk 1.92, 1.27 to 2.92) indicated that overlearning trains the child to wake in response to the sense of a full bladder and reduces relapse when alarm treatment is stopped.⁴¹

In "arousal training" a child is rewarded for going to the toilet within three minutes after the alarm rings, which enhances motivation and improves outcome. According to a small trial, this method had a higher success rate than rewarding for a dry bed or no rewards (98% v 73% and 84%; $P < 0.001$).⁴⁵ Other methods, such as dry bed training (an intensive programme that combines rewards, aversive behavioural interventions, drinking, voiding, and waking routines with or without alarm training), are no more effective than alarm monotherapy.⁴⁶

What are the options for medical therapy?

Desmopressin

Desmopressin has been used to treat nocturnal enuresis for the past 40 years. It is a synthetic analogue of the pituitary hormone, arginine vasopressin, and it reduces urine production by increasing water reabsorption by the collecting tubules. Desmopressin was initially available as a nasal spray. Newer oral preparations (tablet or lyophilisate melt)

TIPS FOR NON-SPECIALISTS

Alarm training and desmopressin are both first line treatments for nocturnal enuresis depending on parent and child motivation and the social situation. If one does not lead to continence, a switch to the other may be effective

Alarm training is usually tried first if the child is motivated to become dry and has sufficient support from the family

Try desmopressin first if the child needs an effective short term solution or does not have sufficient motivation or family support for alarm training

In non-monosymptomatic nocturnal enuresis, treat lower urinary tract symptoms (and underlying constipation) with urotherapy before treating the enuresis. Add anticholinergics if the child has signs of overactive bladder (urinary frequency or urgency)

In refractory cases, a thorough reassessment of adherence to treatment, diagnosis of daytime bladder symptoms, and behavioural and emotional disorders can be helpful

Expected bladder capacity is calculated by: (age in years +1) × 30 mL in children 2-12 years of age. If the largest void during the day is significantly smaller than the expected bladder capacity, this may indicate poor fluid intake, constipation, or overactive bladder syndrome

Use bladder diaries to detect nocturnal polyuria, because this affects treatment

have a lower risk for water intoxication than the nasal formulation.⁴⁷ Desmopressin is particularly effective for short term use when a rapid response is needed, such as when the child is going for a sleepover or school camp. It is also useful when alarm training is difficult or contraindicated (when parents are not supportive), or in conjunction with other treatments in treatment resistant situations.⁴⁸

The drug is well tolerated—side effects (such as headaches, abdominal pain, and emotional disturbances) are uncommon. The rare but potentially serious side effect of water intoxication and hyponatraemia is minimised when children restrict drinking after taking desmopressin. It is advisable to withdraw desmopressin regularly (such as every three months) to assess the ongoing need.²²

In a systematic review of 47 trials, desmopressin (standard dose) had some effect during treatment in about 70% of children. Most experienced a reduction in the amount and frequency (by one to two nights/week) of bedwetting compared with placebo (weighted mean difference (WMD) -1.33, -1.67 to -0.99), although less than half became completely dry (relative risk for failure 0.81, 0.74 to 0.88).⁴⁸ The relapse rate was high, with no difference between desmopressin and placebo, and only 18-38% remained dry when the drug was discontinued. Desmopressin is licensed for treating nocturnal enuresis in children over 6 years of age in more than 100 countries, although the nasal formulation was withdrawn for the treatment of this condition in 2007 because of a significantly higher incidence of symptomatic hyponatraemia compared with oral desmopressin.

Imipramine

A systematic review of 58 trials showed that imipramine and other tricyclic antidepressants can be effective,⁴⁹ with

ADDITIONAL EDUCATIONAL RESOURCES

All the following resources are useful for patients and healthcare professionals. Each resource has simple explanations and summaries written for consumers, as well more detailed information with references to the evidence for healthcare professionals. All are free unless stated otherwise

National Institute for Health and Care Excellence. Nocturnal enuresis. CG111. 2010.

www.nice.org.uk/nicemedia/live/13246/51367/51367.pdf

Cochrane Library

(www.thecochranelibrary.com/view/0/index.html)—

Seven systematic reviews of various treatments for nocturnal enuresis are available on this site (free in some countries)

International Children's Continence Society

(www.i-c-c-s.org/)—Additional resources for members

Education and Resources for Improving Childhood Continence (www.eric.org.uk/)

Australian Continence Exchange

(www.continenceexchange.org.au/)

AREAS FOR FUTURE RESEARCH

Better understanding of sleep arousal defects

Effective strategies for treating resistant nocturnal enuresis and sleep arousal defects

a reduction in the frequency of bedwetting by one night per week compared with placebo (WMD -0.92, -1.38 to -0.46). About a fifth of the children became dry while on treatment (relative risk for failure 0.77, 0.72 to 0.83). This effect was not sustained after treatment stopped, with no difference between tricyclics and placebo (relative risk 0.98, 0.95 to 1.03). Imipramine is approved for use in treating nocturnal enuresis in children aged 6 years and above. Owing to possible side effects of cardiac arrhythmias, hypotension, hepatotoxicity, central nervous system depression, interaction with other drugs, and the danger of intoxication by accidental overdose, tricyclics are used for treating resistant cases only. The NICE guideline advises increasing or decreasing the dose of imipramine gradually, with electrocardiographic monitoring if high doses are prescribed.²² In the systematic review, the data comparing tricyclics with desmopressin were inconsistent.⁴⁹

Anticholinergic drugs

Anticholinergic drugs have a potential role, mainly in non-monosymptomatic nocturnal enuresis. They are thought to act by treating the underlying overactive bladder, thereby increasing the storage capacity of the bladder. Although anticholinergic monotherapy is ineffective, it can improve treatment response when combined with other established treatments, such as imipramine, desmopressin, or enuresis alarms, particularly in treatment resistant cases.⁵⁰ For example, in a systematic review, a meta-analysis of two small trials showed that oxybutynin combined with imipramine was superior to imipramine monotherapy, with improved treatment response (relative risk 0.68, 0.50 to 0.92) and reduced relapse rates (0.48, 0.31 to 0.74).⁵⁰ In the same review, a meta-analysis of

another two small trials showed that oxybutynin combined with desmopressin was superior to desmopressin monotherapy in refractory monosymptomatic nocturnal enuresis.⁵⁰ Cohort studies found that the newer anticholinergic drugs (tolterodine, solifenacin, propiverine) have fewer side effects, with variable efficacy compared with oxybutynin,⁵¹⁻⁵³ but some are not licensed for children or are not available in all countries, and specialist opinion should be sought regarding these drugs.

Complementary and alternative therapies

Complementary and alternative therapies can be used instead of pharmacotherapy for nocturnal enuresis, although the evidence for their effectiveness is limited by low quality studies.⁵⁴ Acupuncture and hypnotherapy show the most promise. A systematic review of acupuncture compared with other treatments found that acupuncture seems to be as effective as desmopressin and more effective than no treatment.⁵⁵ In one small randomised controlled trial, hypnotherapy appeared to be as effective as imipramine (relative risk 0.95, 0.68 to 1.32), with a lower relapse rate after cessation of treatment (0.08, 0.01 to 0.56).⁵⁶

Psychological treatments

Because children with nocturnal enuresis have an increased risk of behavioural or psychological disorders, psychological treatments have a role in enuresis, particularly in the presence of treatment failure and comorbid disorders. ICCS recommends psychological screening of children with nocturnal enuresis using validated parental questionnaires.² When marked symptoms are present, a full child psychological or psychiatric assessment is rec-

ommended. If a behavioural or emotional disorder (such as attention-deficit/hyperactivity disorder) is diagnosed according to ICD-10 (international classification of diseases, 10th revision) or DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*, fifth edition) criteria, evidence based counselling and treatment are recommended. The NICE guideline concludes that there is no evidence to justify the cost of psychotherapy for enuresis if no clinically relevant psychological disorder is present. The main treatment goal in these cases is symptom oriented treatment of enuresis only. NICE recommends treating comorbid disorders, because this is thought to help improve adherence to the enuresis treatment.²²

What is the prognosis for nocturnal enuresis?

According to large epidemiological studies, nocturnal enuresis decreases with age, with a spontaneous remission rate of about 15% per year.^{3 24} A large cohort study found that children with more severe forms of enuresis and those with non-monosymptomatic enuresis are more likely to have persistent problems,²⁴ and treatment for these children should not be delayed. Importantly, nocturnal enuresis can improve with treatment, and improved self esteem and quality of life have been reported after successful treatment.²⁶ It is therefore important to offer timely treatment, and to refer children for specialist care when treatments are not effective.

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References are in the version on bmj.com.

ANSWERS TO ENDGAMES, p 38 For long answers go to the Education channel on bmj.com

PICTURE QUIZ An unusual case of quadriparesis

- 1 A hyperintense triangular lesion in the central pons with peripheral sparing. In the clinical context of spastic quadriparesis, this is consistent with central pontine myelinolysis.
- 2 The most common cause of central pontine myelinolysis is the rapid correction of hyponatraemia. Chronic alcohol misuse and malnourishment predispose patients to this condition. Other associations include peritoneal dialysis, liver failure, advanced lymphoma, dehydration, and the discontinuation of drugs that can cause the syndrome of inappropriate antidiuretic hormone secretion, such as desmopressin, carbamazepine, and selective serotonin reuptake inhibitors.
- 3 The treatment of central pontine myelinolysis is supportive, with cautious correction of electrolyte disturbances. When medically stable, prolonged rehabilitation may be needed.
- 4 Serum sodium concentrations should not be corrected by more than 6-8 mmol/L in any 24 hour period. High risk patients, such as those with severe hyponatraemia (≤ 120 mmol/L) or comorbidities including alcoholism and malnutrition, should be treated more cautiously, and a correction rate of 4-6 mmol/L in 24 hours is recommended.
- 5 The prognosis is highly variable, ranging from death or severe disability to full neurological recovery.

STATISTICAL QUESTION

Convenience sampling

Statements *a*, *b*, and *c* are all false.