Nocturnal enuresis

By Gillian Knott

Case study

Mrs RJ brings her six-year-old son Kaden into the pharmacy and asks for some advice. Kaden has been wetting the bed since he was a baby. Although he goes to the toilet during the day with no problems, he is wetting the bed at night at least twice a week. Mrs RJ is getting concerned about his inability to control the problem. Not only is she concerned that there may be something seriously wrong with Kaden, but with two younger children, the disruptions to sleep and the extra work in washing bedclothes and sheets are not helping. Kaden is in year one at school and it is starting to cause some embarrassment as she does not want to send him on sleepovers for fear of him wetting the bed. Going on holidays can also be stressful. Mrs RJ is careful to make sure that Kaden goes to the toilet just before bed and she has a plastic mattress protector on his bed.

Mrs RJ has heard that there are treatments available that can help with this problem, and asks what we can suggest for Kaden.

Introduction

Although nocturnal enuresis (or ‘bedwetting’) is common in young children, it is regarded in the majority of cases as part of the normal process of developing continence. It can, however, have a significant psychological impact on a young child, both emotionally and socially, and may be associated with feelings of helplessness, guilt, shame and loss of self esteem. Parents or carers may feel angry and frustrated as they do not know how to help their child and will often turn to a health professional for advice.

Epidemiology

Nocturnal enuresis (NE) is defined as the involuntary discharge of urine while asleep at night. It commonly occurs in children aged five years or older in the absence of congenital or acquired defects of the central nervous system or urinary tract.1 Studies have found that the incidence of NE is higher in boys than in girls,3 and is more common in those with a family history.2 It affects 15–20% of five-year-olds, 5% of 10-year-olds, and 1–2% of people aged 15 years or over.1 In 1996, an Australian study found that 18.9% of children between five and 12 years experienced NE, with 5.1% wetting the bed at least once a week and 2.4% wetting the bed every night. It is estimated that without treatment, around 15% of affected children become dry each year.1 NE can persist into adulthood, with about 0.5% of adults continuing to have episodes of NE.2 In adults, however, there is no natural trend towards reduction in symptoms with age.5
Pathophysiology

The process of micturition is under the influence of the cerebral cortex. A conscious sensation of bladder filling normally develops between the ages of one and two years. The majority of children achieve bowel control by the age of two to three years and urinary control at around three to four years. By the age of five, more than 90% of children are continent during the day, but night-time continence will generally take longer to achieve. For this reason, NE is not diagnosed in children under five years of age, and generally treatment is not considered until the age of seven years.

There are two main phases of micturition: the storage phase and the voiding phase.

Storage phase

In the storage phase, the bladder gradually fills with urine until it reaches a certain size or capacity, after which a feeling of fullness develops and a desire to void is felt. A child’s bladder capacity slowly increases with age during the first 12 years of life. An estimated normal bladder capacity for children 0–12 yrs is about (age x 30 mL) + 30 mL (e.g. for a six-year-old child, this would be 210 mL). The normal bladder capacity for children 0–12 yrs is about (age x 30 mL) + 30 mL (e.g. for a six-year-old child, this would be 210 mL).

Voiding phase

At maximal bladder capacity, the perception of fullness triggers the voluntary process of voiding via signals to and from the cerebral cortex. This leads to the relaxation of the pelvic floor muscle and the external urethral sphincter, along with contraction of the detrusor muscle surrounding the bladder, resulting in emptying of the bladder.

Frequency of voiding will be influenced by functional bladder capacity: in adults and children, normal frequency is between four and seven times a day or every two to three hours. There is a 50% reduction in urine production at night due to the circadian effect of the antidiuretic hormone (ADH). This accounts for the normally reduced frequency of nocturnal voiding.

Diagnosis and causes

Nocturnal enuresis may be diagnosed as primary or secondary. In primary enuresis, children have never achieved urinary continence for more than six months. Secondary NE is less common, and in these children bedwetting develops after the patient has previously been dry for at least six consecutive months.

Risk factors for primary NE include family history, nocturnal polyuria, impaired sleep arousal and bladder dysfunction. Secondary enuresis is more likely to be associated with pathology such as UTIs, type 1 diabetes, constipation or psychological factors. In secondary NE, an identifiable cause or trigger is more likely to be found.

Nocturnal enuresis may also be categorised as monosymptomatic (occurring only during sleep with no daytime symptoms) or non-monosymptomatic (bedwetting at night which is also associated with daytime incontinence or bladder symptoms). Daytime incontinence is defined as uncontrollable leakage of urine during the day, which may be continuous or intermittent. Daytime bladder symptoms include urgency and/or frequency, and may occur with or without incontinence. Children with NE along with daytime wetting problems should be diagnosed as incontinent, as the nocturnal enuresis is part of the overall incontinence.

Monosymptomatic NE is the most common form of enuresis and accounts for 85% of cases. Non-monosymptomatic NE is more likely to have an organic cause.

The three system model of nocturnal enuresis defines NE as a mismatch of three factors, namely excessive nocturnal urine production, nocturnal bladder overactivity along with an inability to arouse to bladder sensations.

About two-thirds of children with NE have increased nocturnal urine output which is mainly due to an insufficient night-time rise in anti-diuretic hormone (ADH) production. This leads to nocturnal polyuria and bedwetting of a large volume of dilute urine.

Overactivity of the bladder can have several possible causes including instability of the detrusor muscle, bladder irritation (e.g. due to constipation, urinary tract infection) or neurological dysfunction. Symptoms associated with an overactive bladder may include urgency and/or frequency, urge incontinence (involuntary loss of urine associated with a strong urge to void) and wetting more than once a night. Some children have normal daytime bladder activity but may have overactivity at night. This can lead to reduced functional bladder capacity at night and subsequent NE.

Some children can also have bladder emptying problems due to urethral sphincter or pelvic floor overactivity. Constipation in children can have a significant effect on bladder function leading to bladder overactivity, incomplete bladder emptying and an increased risk of urinary tract infections. Parents are often unaware that their child has constipation; it is estimated that 34% of children with chronic constipation and encopresis (faecal soiling) have NE.

All children with NE have arousal problems which prevent them from waking in response to a full bladder.

Refer to Table 1 for a summary of possible causes of NE.

Assessment of nocturnal enuresis

As pharmacists, our major role in assessing NE is to determine if referral is warranted. The decision to refer would be based on the patient’s symptoms and medical history, the age of the child, the severity of the symptoms as well as the degree of concern exhibited by the parent. Questions which may be asked of the patient or parent may include:

- How old is the child?
- Have they previously been dry for six months or more?
- If NE is secondary, have there been any specific events which may have triggered the symptoms, e.g. problems at school, stressful events?
- How often does the child wet the bed? How much urine? (Severe NE is defined as more than three wet nights per week.)
- How often do they urinate during the day? Approximate daily fluid intake?
- Are there any other associated symptoms? (e.g. urgency, frequency, problems with urinary flow)
- Are they taking any medications? (e.g. diuretics, sodium valproate)
- Are there any medical conditions? (e.g. constipation, sleep apnoea)
- Any allergies?
Managing nocturnal enuresis

Managing NE will initially be based on identifying any specific causes or predisposing factors. Frequently, no cause can be identified. Available treatments include behaviour therapy, alarm therapy and pharmacological therapy. In all management plans, it is important that the child has an active role and that both child and carer are counselled thoroughly on the cause and usual prognosis of NE. This will help to demystify NE and remove any blame and guilt that the child may have, as well as provide some reassurance for the parent or carer.

It is important to remember that bedwetting is not the child’s fault and that disciplining children and young people because they have wet the bed is not advised. 6

1. Behaviour therapy

Simple behaviour and physical interventions may be all that is required for patients under seven years with primary monosymptomatic NE. More complex behavioural and educational interventions such as dry bed training have also been used, but require the time and commitment of both the patient and their family to achieve significant results. 5 Evidence for efficacy of behavioural therapy is lacking, however, clinical experience suggests that this approach may be beneficial. 3

The use of training programs that involve either ‘holding on’ and waiting before urinating or stopping the flow of urine are not recommended as they have not been shown to be effective. 6

Refer to Table 2 for some suggested behavioural strategies and advice.

2. Alarm therapy

Enuresis alarms have been found to be the most effective treatment for enuresis. 11 Alarms are recommended as first line therapy in children who have not responded to advice on fluids, toileting or an appropriate reward system. 5

An enuresis alarm is activated when urine makes contact with the device’s sensor. It is thought that the alarm works by changing the signal that promotes urination into an inhibitory signal or a waking signal. 5
In Australia, two types of alarms are available:

• a pad and bell alarm, where a child lies on a large pad placed in the bed and any liquid triggers the alarm; and

• a personal alarm, which is attached to the underpants of the child or to a continence pad inside the child’s underpants.

These alarms are extremely sensitive and require only a few drops of liquid to be activated. In comparative studies, a 65% success rate was found with alarm treatment (success defined as 14 consecutive dry nights), however, 42% of children relapsed after ceasing alarm treatment.12 Children with frequent bedwetting are more likely to have success with alarms due to the greater opportunities for practice.5

Alarms may not be suitable for all patients. Disadvantages are that they usually take about six to eight weeks to work and may be disruptive to other family members, who may also be required to assist the child when the alarm goes off. Records need to be kept of when a child wakes to the alarm and how wet the bed is.6 It is recommended that if there is no improvement after one month of therapy it should be discontinued.

3. Pharmacological therapy

Desmopressin

Desmopressin is a synthetic analogue of vasopressin, also known as anti-diuretic hormone (ADH). It increases water reabsorption in the kidney via the collecting ducts, resulting in increased urine osmolality with a concurrent decrease in urine output.9 In Australia, it is available on PBS authority prescription for the treatment of primary nocturnal enuresis in children from six years of age for whom an enuresis alarm is contraindicated or ineffective.9 It is available as a tablet, a nasal spray and a sublingual wafer (melt).

In terms of efficacy, about 70% of children have at least a 50% reduction in number of wet nights while using desmopressin.5 In most patients, however, the effect is not sustained on cessation of the drug.2,5 In comparison to alarm therapy, desmopressin is about 30% less effective in the treatment of bedwetting, and about 70% less effective in preventing relapse after stopping treatment.4 An enuresis alarm in combination with or alternating with desmopressin may be effective in children resistant to treatment with an alarm or desmopressin alone.1,6

When compared to alarm treatment, desmopressin has the advantage of having a more immediate action, being easy to administer and not disruptive to sleep for other family members.

Common adverse effects of intranasal desmopressin include nosebleeds and mild abdominal pain. Of particular concern in recent years has been the less common risk of hyponatraemia, which has been associated mainly with the use of the nasal spray.16 In the presence of excessive fluid intake, water retention can lead to a dilutional hyponatraemia, which can progress to cerebral oedema, nausea, vomiting, headache, confusion and possible seizures.14

The majority of reported cases of hyponatraemia with the nasal spray appear to be related to misuse, overdosing or excessive fluid intake.7 Nevertheless, in both the US and UK, the nasal spray is no longer recommended for primary nocturnal enuresis. In Australia, after receiving numerous reports of hyponatraemia, the Therapeutic Goods Administration recommended in 2007 that desmopressin nasal spray only be used for nocturnal enuresis if the oral or sublingual route is inappropriate.14 Avoidance of excessive fluid intake should also be advised during treatment. It is recommended that children only take enough fluid to quench thirst from one hour before to eight hours after the dose.13–15

Initial treatment with desmopressin should be for one to three months, followed by withdrawal to assess for relapse.13 Long term use should only be considered with periodical review to assess effect.14

Tricyclic antidepressants

Tricyclic antidepressants, particularly imipramine (less commonly amitriptyline or nortriptyline), have been found to cure bedwetting in 20% of children.4 They have an anticholinergic action resulting in relaxation of the bladder and improved bladder capacity.13 As with desmopressin, most children will relapse following cessation of therapy. Tricyclic antidepressants are no longer recommended for the treatment of childhood enuresis due to the high incidence of adverse effects, including potentially serious cardiac effects and toxicity in overdose.11,13

Anticholinergic drugs

In some children with non-monosymptomatic NE, anticholinergic drugs such as oxybutynin and tolterodine may be effective in improving bladder capacity or reducing detrusor overactivity.3 These medications are generally used by specialist urologists in older children, as evidence of effectiveness and safety for NE is limited.13 Some children may benefit from a combination of desmopressin and an anticholinergic. If this combination is used, the child should be monitored for signs of constipation and urinary retention, which may worsen enuresis.3 Due to their additive anticholinergic effects, the combination of a tricyclic antidepressant and an anticholinergic drug is not recommended.6

Reboxetine

The antidepressant reboxetine, a noradrenaline reuptake inhibitor, is pharmacologically related to imipramine, but appears to have no cardiovascular toxicity. There is limited evidence that reboxetine may be effective in children with therapy resistant NE, however, further studies are required to confirm its role in practice.3,17

Other non-pharmacological interventions

Other non-pharmacological interventions for NE include psychotherapy, acupuncture or laser acupuncture,1 hypnosis,1 and transcutaneous parasacral electrical nerve stimulation.8 There are limited studies to support these treatments for NE. Products such as pull-up pants and bed protectors are available from pharmacies and various supermarkets and department stores and may be helpful to minimise the impact of bedwetting on family life. However, children may become used to the protection of these devices and this may delay the development of continence.5
Case study

Mrs RJ was counselled on the causes and likely course of NE. She was reassured that as Kaden was still only six years old, his bedwetting was likely to improve over time, and that at this stage, based on his current symptoms and history, medical treatment may not be necessary. She was counselled on the various behavioural strategies recommended for bedwetting, and the treatment options that were available if Kaden’s problem persisted. She was also advised that if she was still concerned, she may wish to consult her GP for further investigation and to discuss treatment.

This verbal advice was supplemented by some written information on bedwetting and suggested websites where she could obtain further information.18–20

Key practice points

- Nocturnal enuresis is a common problem in children but in the majority of cases will clear over time without treatment.
- The psychological impact of bedwetting on the child and the family can be significant and must be considered when deciding on appropriate treatment.
- Behavioural strategies and education may be the only treatment required for children under seven years of age with primary monosymptomatic NE.
- Enuresis alarm therapy is the most effective treatment for nocturnal enuresis with the lowest relapse rate. Desmopressin is an effective second line treatment, however, the risk of hyponatraemia must be considered.
- Although they may be effective, tricyclic antidepressants are no longer recommended for nocturnal enuresis due to problems with side effects and toxicity.

Questions

1. What percentage of five year old children are estimated to be affected by nocturnal enuresis?

- a) 0.5%.
- b) 1–5%.
- c) 5–10%.
- d) 15–20%.
- e) 30%.

2. According to the three system model, what are the three main factors that can lead to nocturnal enuresis?

- a) Nocturnal polyuria, bladder dysfunction and impaired sleep arousal.
- b) Nocturnal polyuria, constipation, bladder dysfunction.
- c) Nocturnal polyuria, constipation, impaired sleep arousal.
- d) Bladder dysfunction, impaired sleep arousal, psychological stress.
- e) Bladder dysfunction, Type 1 diabetes, psychological factors.

3. Which of the following statements regarding the use of desmopressin for nocturnal enuresis is CORRECT?

- a) Desmopressin is a synthetic analogue of vasopressin and acts by decreasing water reabsorption in the kidneys.
- b) Desmopressin is about 70% less effective than alarm therapy in the treatment of nocturnal enuresis.
- c) The effect of desmopressin is normally sustained on cessation of the drug.
- d) In Australia, desmopressin nasal spray is indicated in children with nocturnal enuresis only when the oral or sublingual route is inappropriate.
- e) Children using desmopressin should restrict fluids from three hours before to eight hours after the dose.

4. Which of the following statements regarding alarm treatment for nocturnal enuresis is CORRECT?

- a) It is thought that alarm treatments work by converting the signal to promote urination to one of inhibition of urination or of waking.
- b) An advantage of alarm treatments is that they work quickly to relieve symptoms.
- c) The bedwetting relapse rate with alarm treatments is much higher than with desmopressin treatment.
- d) A large amount of urine is required to trigger an enuresis alarm.
- e) Alarm treatments should be discontinued if there is no response within one week.

5. Which of the following is NOT recommended as a behavioural strategy to assist a child with nocturnal enuresis?

- a) Fluid restriction for two to three hours prior to bed.
- b) Training programs that involve ‘holding on’ and waiting before urination.
- c) Rewards for dry nights, e.g. a bedwetting chart for a young child.
- d) Avoidance of constipation.
- e) Avoiding caffeine-containing and carbonated drinks.