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Evidence based paediatrics

Evidence based management of nocturnal enuresis

Jonathan H C Evans

THE CASE A 10 year old boy has been brought to see you because of bedwetting. He is dry during the day. The only treatment he has had ever is desmopressin once when he was away at a camp for two nights. He was dry both nights but he slept very little, and his parents are not sure whether the desmopressin was responsible for his dry nights. Normally he is wet most nights. His parents realise that the wetting is now beginning to upset the boy and both he and they are requesting help. Nothing of note is found on examination and on urine culture.

Summary points

- Daytime urinary symptoms in a bedwetting child suggest an underlying bladder dysfunction rather than nocturnal enuresis
- Enuresis alarms are effective and safe treatment but require several months of continuous use and are therefore unsuitable for some families
- Desmopressin and imipramine both improve bedwetting but there is no good evidence of lasting benefit after treatment is stopped
- Imipramine has high frequency of serious adverse effects and should be used with great caution
- The parents and child should actively participate in the choice of treatment

Background

Bedwetting is a common symptom with many causes.[1] Nocturnal enuresis is the most frequent cause; it is recognised by the absence of other urinary symptoms or signs of disease. Most children presenting with nocturnal enuresis have never been reliably dry, but in a minority enuresis has started after they had become dry, possibly triggered by stressful life events. If daytime wetting is present the child is most likely to have the urge syndrome, with or without urge incontinence as well, or dysfunctional voiding—functional bladder disturbances that result in incontinence. Rarely, incontinence may be due to structural abnormalities of the urinary tract, such as posterior urethral valves, or abnormalities of the nervous system, such as spinal dysraphism.

A variety of factors contribute to the development of nocturnal enuresis; genetic factors and stressful early life events are the most notable. Physiological disturbances such as nocturnal polyuria, small functional bladder capacity, and decreased arousal response to the full bladder have also been identified. Most children will eventually outgrow their enuresis but this may take several years, and thus treatment is indicated for children who are adversely affected by the wetting.

This is the fourth in a series of five articles

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Treatment options

This child seems to have nocturnal enuresis. You judge that his parents are supportive and that the most important outcome is for him to become dry in the long term. There are a number of therapeutic options that are widely used.

Enuresis alarms, which wake the child in the night at the onset of wetting, are a form of conditioning that may require several months of continuous use. Treatment is thus arduous.

Dry bed training refers to regimens that include enuresis alarms, waking routines, positive practice, cleanliness training, bladder training, and rewards, in various combinations.

Star charts are used as a record and incentive scheme, either alone or with other treatments.

Desmopressin is a synthetic analogue of antidiuretic hormone that reduces nocturnal urine output. It has a rapid onset of action, making it suitable for use in the short term. It can be used alone or in combination with an enuresis alarm.

Imipramine is a widely used tricyclic antidepressant. The mechanism of its action in enuresis is not fully understood, but it has anticholinergic and antidiuretic actions as well as effects on the central nervous system.

Oxybutinin, an anticholinergic drug, is used in the treatment of incontinence due to detrusor overactivity. It may therefore have a role in the treatment of bedwetting when detrusor overactivity is a factor.

Finding the evidence

You formulate a series of structured questions about the effectiveness of different interventions for enuresis.

(1) In children of school age with nocturnal enuresis (population), does an enuresis alarm (intervention) lead to fewer wet nights in the long term (outcome)?

(2) In children of school age with nocturnal enuresis (population), does dry bed training (intervention) lead to fewer wet nights in the long term?

(3) In children of school age with nocturnal enuresis (population), does using star charts (intervention) lead to fewer wet nights in the long term with the least side effects (outcome)?

(4) In children of school age with nocturnal enuresis (population), does imipramine or does desmopressin (intervention, comparison) lead to fewer wet nights in the long term (outcome)?

(5) In children of school age with nocturnal enuresis (population), does oxybutinin lead to fewer wet nights than placebo (intervention, comparison) in the long term (outcome)?

(6) In children of school age with nocturnal enuresis (population), does combination treatment with a drug and enuresis alarm or an alarm alone (intervention, comparison) lead to fewer wet nights (outcome)?

Ideally you want to find a systematic review of randomised controlled trials that summarises all the relevant data available. You start by looking in *Clinical Evidence*, a compendium of evidence on the effects of interventions in health care, and find that it has a chapter on nocturnal enuresis.[2] The chapter summarises the evidence and provides references. You want more detail, so you decide to read the systematic reviews that are referenced, one by Lister-Sharpe et al and two reviews from the Cochrane Library by Glazener and Evans. You find one further systematic review by Houts et al among the references of the other systematic reviews. These all appear to be thorough, properly conducted reviews. So you use these as your major source of information.[3–6]

Alarms, dry bed training, and star charts

Children given alarms were 13 times as likely to become dry as children without alarms (relative risk 13, 95% confidence interval 5.6 to 31) but between 29% and 69% of children relapse after initially successful treatment. The dropout rate varied from 0% to 26%. Dry bed training with an alarm is as effective, but not more so, than an enuresis alarm alone (1.1, 0.7 to 1.8). It is ineffective without an alarm. Dry bed training plus an alarm is more likely than dry bed training alone to achieve dryness (4.1, 2.2 to 7.9). Unfortunately, neither review identified any controlled trials of star charts.

Summary of effective treatments for nocturnal enuresis

Question	Type of evidence	Positive effects	Negative effects
No treatment	One systematic review, total of 20 trials	10% get dry (within weeks), 2% remain dry	Poor self esteem
Enuresis alarm	Two systematic reviews, total of 46 RCTs	Beneficial in the short and long term	Hard work. Poor motivation and adverse family circumstances reduce effectiveness
Dry bed training (with alarm)	One systematic review, total of 4 RCTs	As effective as alarm alone	Ineffective without alarm. Hard work
Alarm and desmopressin	One RCT (76 patients)	Better than alarm alone if adverse factors for successful treatment are present	Involves drug and alarm
Desmopressin	Two systematic reviews, total of 15 RCTs	Beneficial while drug is taken	Relapse usual when treatment finishes Adverse effects rare; nasal irritation (1.5%) most common
Imipramine	Two systematic reviews, total of 28 RCTs	Moderate benefit while drug is taken	Relapse usual when treatment finishes. Important side effects involving central nervous system are common (3%). Drug is lethal in overdose
Desmopressin *v* imipramine	One RCT	No difference in effectiveness	Adverse effects are more serious with imipramine
Oxybutinin	Two poor quality RCTs, one non-randomised study	Conflicting results; may be of benefit in children with bladder instability, particularly in combination with desmopressin	Anticholinergic adverse effects in up to 17% of patients

RCT=randomised controlled trial.

Drug treatment

Desmopressin

Children given desmopressin have 2.2 (0.7 to 3.7) fewer wet nights per week than those receiving placebo, and they are 4.5 (1.4 to 15) times more likely to become dry. After treatment is stopped, however, the mean number of wet nights at follow up is no different in the placebo group (relative risk 0.14, – 1.1 to 1.35).

Tricyclic antidepressants

Children taking imipramine have 1.3 (0.7 to 1.8) fewer wet nights per week and are 4.2 (1.2 to 15) times as likely to become dry as those receiving placebo. However, there are no reliable data on whether they remain dry after stopping treatment.

Imipramine compared with desmopressin

One randomised controlled trial involving 36 children compared desmopressin directly with imipramine. The effects of the two drugs did not differ either during treatment or at follow up six weeks after treatment was stopped. The mean difference in wet nights per week was – 0.1 (– 1.5 to 1.3) on treatment and – 0.2 (– 1.6 to 1.2) at follow up. The wide confidence intervals indicate that the trial could have missed quite large differences in effectiveness. From this one small trial you draw the tentative conclusion that desmopressin and imipramine have similar effectiveness, and you therefore evaluate the data on adverse effects in order to determine which is the better choice.

Adverse effects of tricyclic antidepressants and desmopressin

The frequency of adverse events was reviewed by Glazener and Evans.[4 5] There were 17.3 adverse events per 100 children receiving a tricyclic antidepressant, compared with 7.1 per 100 children receiving desmopressin. There were no life threatening events or deaths. Nasal irritation or nosebleeds associated with the nasal application of desmopressin accounted for half its adverse effects. Desmopressin also has one rare but serious adverse effect, water intoxication causing coma and seizures. There are no studies reporting the frequency of this event, but one report identified 21 cases in the literature up until 1992.[7]

With tricyclic antidepressants, central nervous system effects such as drowsiness, lethargy, agitation, depression, and sleep disturbance accounted for most adverse effects, and gastrointestinal upsets accounted for the remainder. Rare adverse effects such as seizures, cardiac arrhythmias, and accidental deaths from overdose have also been reported.

Oxybutinin

One placebo controlled trial of oxybutinin for primary nocturnal enuresis reported no significant benefit and noted minor side effects in 5 of 30 (17%) subjects.[8] A high dropout rate (25%) and insufficient statistical data mean that you cannot confirm or refute the conclusion of the study.

Another controlled trial compared oxybutinin with dicycloverine (dicyclomine) in 29 children, but again statistical details were sparse, making it impossible to confirm or refute the authors' conclusion that oxybutinin was superior to dicycloverine.[9]

Combination therapy

One randomised controlled trial involving 30 children gave information on the number of children becoming dry: the two groups did not differ (RR 0.67, 0.67 to 1.64). One further trial has been published since the review.[10] This trial, involving 76 children, compared desmopressin plus an alarm with an alarm alone and showed that 76% of children receiving combination therapy became dry compared with 46% of those using the alarm, with similar relapse rates in the two groups (15% and 19%).

Conclusions

Patients with primary nocturnal enuresis, no daytime wetting, no apparent psychological problems, and with supportive parents have a good prognosis with the use of either desmopressin or an alarm. A detailed voiding history, supported by a frequency and volume chart, will be helpful in determining with more confidence that neither bladder instability nor dysfunctional voiding is present. The current home circumstances must be suitable for the use of an alarm. The evidence is summarised in the table.

Applying the evidence

This patient seems to be a good candidate for treatment with an alarm, and he will be at least 13 times more likely to become dry if treated than if not treated. He has a good chance of remaining dry in the long term, but the treatment will require considerable effort and persistence. It is likely that he would also become dry on desmopressin, but he would then have only a small chance of remaining dry after treatment. Since he is likely to do well with an alarm, adding desmopressin is unlikely to improve the long term outcome. With imipramine treatment he would be four times more likely to become dry than without it, but the long term benefit is uncertain and there is a risk of serious central nervous system or gastrointestinal adverse effects. There are no data to support the use of oxybutinin. The most suitable option for this child is thus treatment with an enuresis alarm. If a rapid effect is needed, or if the child's circumstances indicate that the necessarily prolonged use of an alarm is undesirable or not possible, then desmopressin would be the better option.

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