



# Therapeutics Today

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## ***How to manage nocturnal enuresis in children and young people.***

Bedwetting is a widespread and distressing condition that can have a deep impact on a child or young person's behaviour, emotional wellbeing and social life, as well as causing stress to the parents or carers. A recent guideline (CG111) from the National Institute for Health and Clinical Excellence ([www.nice.org.uk](http://www.nice.org.uk)) dealt with its management. The guideline defines bedwetting as involuntary wetting during sleep (without referring to frequency or pathophysiology). The prevalence of bedwetting decreases with age: bedwetting <2 nights/week has a prevalence of 21% at 4.5 years falling to 8% at 9.5 years. More frequent bedwetting is less common (prevalence of 8% at 4.5 years; 1.5% at 9.5 years). Assessment is important in determining possible causes; **the typical pattern is of voiding of a large volume of urine in the first few hours of the night**. Less frequent patterns - children who pass urine more than once per night, who also have daytime symptoms or who were dry for  $\geq 6$  months before beginning to bedwet - may suggest an underlying problem such as overactive bladder, urinary infection or other urinary condition or recent emotional trauma. The guidance recommends that children / parents should be asked to keep a diary if the pattern is not obvious. **Urinalysis should not be performed routinely** unless the child has started bedwetting recently, has daytime symptoms, or a history, signs or symptoms of urinary tract infection or diabetes mellitus. The history should also check for co-morbidities such as behavioural / emotional problems, learning difficulties, constipation and/or soiling which will impact on management and may indicate the need for specialist referral.

**Initially, non-pharmacological treatments should be used** including: proper fluid intake (neither too much nor too little, typically about 1.0 - 1.5L/day), the avoidance of caffeine-based drinks and the need to encourage the child to use the toilet throughout the day at regular intervals (typically between 4-7 times at spaced out intervals). A reward system may be suggested for those children who abide by these strategies. An important aspect of management is to inform the family that bedwetting is not the fault of the child or young person, therefore punitive measures should not be used. Neither waking nor lifting children during the night is recommended as it has not been shown to promote longterm dryness. An alarm (+/-combined with a reward system depending on the age of the child) may be recommended for those children whose bedwetting has not responded to these measures. The response to an alarm should be assessed at 4 weeks and if a response / early signs of a response are noted, the alarm may be continued until 2 weeks' uninterrupted dryness has been achieved. Use for longer than 3 months should be considered on a case-by-case basis.

**Pharmacotherapy:** desmopressin, given at bedtime, may be offered to children / young people if an alarm is inappropriate or a rapid-onset and/or short-term improvement is a priority of treatment. The dose should be slowly titrated and if, at 4 weeks, there is a response (signs such as smaller wet patches or fewer wet nights / episodes per night), it should be continued for 3 months and then stopped for review. If there is a poor or no response, desmopressin may be given earlier (i.e. 1-2 hours before bedtime) and the effect reviewed. If this doesn't work, desmopressin should be stopped and the child referred for specialist opinion. **After specialist assessment**, desmopressin may be combined with an **anticholinergic (e.g. oxybutynin)** for non-responders to prior therapies or those with daytime symptoms. **Imipramine monotherapy** (not licensed in Ireland) may also be advised after specialist assessment. **Imipramine should not be combined with an anticholinergic agent**. In each case, treatment should be reviewed after 3 months (it is recommended to withdraw imipramine gradually). Repeated doses are possible on a case-by-case basis. [Editor's note: a quick reference guide with helpful flowcharts is available online at: <http://guidance.nice.org.uk/CG111/QuickRefGuide/pdf/English>]



### **Does longterm benzodiazepine usage affect cognition in younger adults?**

The acute effects of psychoactive drugs, such as benzodiazepines (BZDs), on cognitive performance (e.g. changes in memory and vigilance) have been well documented. Although BZDs are not recommended for long-term use, observational studies from many countries have confirmed that patients may receive BZDs for several years. A recent article reported on a 10-year follow-up of 1,000 workers (aged 32-62 years) which evaluated the impact of BZD usage on specific cognitive functions (*Eur J Clin Pharmacol DOI 10.1007/s00228-011-1047-y*). This was part of a larger cohort study (n=3,200) looking at the effect of working conditions on health and aging. Data collection (such as lifestyle and medicine use via a self-administered questionnaire) and clinical examination were undertaken at baseline, midway through the study and at study end. BZD usage was divided into non-use, occasional use (<1 year) or long-term use (>1year or reported in >2 questionnaires). Cognitive tests to evaluate memory, visual attention and speed of information processing were administered as part of the clinical examination. Results noted that 3.9% of participants were classified as occasional users of BZD, and 7.5% as long-term BZD users (8.3% of females; 6.7% of males). These results are similar to long-term BZD usage figures reported in other studies. At baseline, females performed better than males on all cognitive function tests. However, by the end of the study, **female long-term BZD users had significantly poorer long-term memory recall compared with their baseline values**; there was no significant decline in the male long-term BZD users. The results were adjusted for lifestyle and medical factors (tobacco use, concurrent disease, behaviour etc) and tests took into account changes due to aging. Because the study needed complete 10-year follow up data, only 1,000 of the 3,2000 subjects from the original cohort were included. However, the authors note that this makes the results more reflective of the "healthy worker" i.e. younger, capable of continuing employment. The authors conclude that further work is needed to see if these adverse effects on cognition, reported with long-term use of BZD in females, might be associated with a risk of developing dementia in old age.



### **Newer-generation antiepileptic drugs and pregnancy**

In addition to being used in epilepsy, antiepileptic drugs (AEDs) are also used for other conditions including bipolar mood disorders, migraine and neuropathic pain syndrome. It is estimated that up to 0.5% of pregnant women take AEDs. The older AEDs (including carbamazepine, valproate, phenytoin) during pregnancy are associated with a 3-fold increased risk of birth defects, however there is little information on the teratogenic effects of the newer AEDs. A Danish population based cohort study assessed the association between fetal exposure to newer AEDs during the first trimester of pregnancy (n=837,795) and the risk of major birth defects (*JAMA 2011; 305: 1996-2002*). In the study, 49 of the 1532 infants who were exposed to lamotrigine, oxcarbazepine, topiramate, gabapentin or levetiracetam during the first trimester were diagnosed with a major birth defect, compared with 19,911 of the remaining 836,263 who were not exposed to an AED (3.2% vs. 2.4% respectively). After adjustment for maternal use of the older generation AEDs during the first trimester and maternal diagnosis of epilepsy before the second trimester, **exposure to these newer AEDs was not associated with an increased risk of major birth defects** (adjusted prevalence odds ratio 0.99; 95% CI 0.72-1.36). There are limitations to the study (e.g. the study did not include information on those who had induced or spontaneous abortions) however the results of the study are in keeping with previous studies of newer generation AEDs. The authors of the study **concluded that based on the currently available evidence, the newer AEDs are not major teratogens although a minor excess in risk cannot be excluded**. [Editor's note: the NMIC can assist with specific drug safety in pregnancy issues through its enquiry answering service]