Nocturnal Enuresis

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The primary reason to diagnose and treat nocturnal enuresis is to achieve dryness. A secondary aim is to improve body image and/or low self-esteem associated with nocturnal enuresis.

Primary outcome measures for therapy of nocturnal enuresis have been defined as follows:

- **Short-term success: dryness for 14 consecutive nights**
- **Long-term success: dryness for 6 consecutive months**
- **Adverse treatment events**

Secondary outcome measures include psychological and quality-of-life assessments.

Summary of evidence for these goals:

- **Alarms achieve dryness for 14 consecutive nights during use in 50–75 % of enuretic children. Half of these maintain dryness when therapy stops.**
- **Desmopressin achieves dryness for 14 consecutive nights in approximately 20 % of treated children. Nearly all resume wetting when therapy stops.**
- **Desmopressin plus tolterodine was more effective than desmopressin plus placebo in one trial enrolling children with mono-symptomatic enuresis who failed desmopressin alone.**
- **Imipramine achieves dryness for 14 consecutive nights in 20–33 % of treated children. Approximately two-thirds relapse when treatment stops after 3 months.**
- **There are few data regarding efficacy of long-term medication use.**
- **Our review found no reports regarding 6-month dryness in treated patients.**
- **Children with enuresis have greater behavioral problems than non-bedwetters. However, successful treatment of enuresis is reported to not impact behavior significantly.**
- **One study reported improved self-concept with treatment.**

Definitions

Infrequent bedwetting: <2 nights per week.

Enuresis: involuntary voiding during sleep ≥2 nights per week for at least three consecutive months and/or causing significant distress/impairment in a child >5 years old without CNS defects (DSM-IV).

Mono-symptomatic nocturnal enuresis: wetting only when asleep.

Non-mono-symptomatic (or poly-symptomatic) nocturnal enuresis: nighttime incontinence associated with daytime symptoms such as incontinence, urgency, and/or frequency.

Secondary enuresis: previously dry for more than six consecutive months.

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Prevalence

Infrequent Bedwetting

Bedwetting <2 nights/week occurs in ≤20 % of 5-year-olds and diminishes to 2 % by 19 years of age.

Infrequent bedwetting is more common in boys than girls.

The Avon Longitudinal Study of Parents and Children (ALSPAC) is an ongoing, prospective, population-based cohort study in the UK that includes 13,973 children born in 1992–1993 and followed at regular intervals. Questionnaires that included questions about enuresis were administered at regular intervals between 54 and 115 months of age. Infrequent bedwetting was present in 22 % at 4.5 years; 16 % at 5.4 years; 13 % at 7.5 years, and 8 % at 9.5 years. Boys had a greater prevalence of infrequent bedwetting than girls at all ages up to 115 months (roughly two times), with identical rates of decline for both males and females. At age 7.5 years, 15 % of boys versus 8 % of girls had infrequent bedwetting, which declined to 10 % of boys at age 9.5 years versus 5 % of girls (Butler and Heron 2008).

In an epidemiologic cross-sectional survey of 16,512 children aged 5–19 years in Hong Kong, bedwetting more than once every 3 months was present in 16 % at 5 years, 10 % at 7 years, and 2 % at 19 years, with boys more likely to have bedwetting than girls at all ages (Yeung et al. 2006).

Mono-symptomatic Nocturnal Enuresis

Enuresis occurs in approximately 8 % of children age 5 years, decreasing to 1–3 % by age 10 years.

Boys have ≥2 times greater risk for enuresis at all ages than girls.

A higher proportion of older children have bedwetting ≥3 nights/week.

Prevalence estimates from 13,973 children in the UK prospective cohort study (ALSPAC) demonstrated enuresis in 8 % of children at 4.5 years, 3 % at 7.5 years, and 1.5 % at 9.5 years. Boys were more likely to have enuresis at all ages than girls (4 vs. 2 % at age 7.5 years) (Butler and Heron 2008).

In the cross-sectional survey of 16,512 children aged 5–19 years in Hong Kong mentioned above, enuresis ≥3 nights/week occurred in 7 % at age 5 years, 3 % at age 7.5 years, and 2 % at age 9.5 years. More frequent bedwetting (≥3 nights/week) occurred in a higher proportion of patients as age increased, such that 82 % of patients with bedwetting aged >10 years had ≥3 wet nights/week versus 42 % of patients aged 5–10 years ($p<0.0001$); 14.3 % of children aged 5 years had enuresis 7 nights/week compared to 48.3 % of 19-year-olds ($p<0.0001$) (Yeung et al. 2006). While bedwetting (infrequent plus frequent) was more common in boys than girls at all ages, data were not gender-stratified for those meeting DSM-IV criteria for enuresis.

Data from 1,136 US children aged 8–11 years in a cross-sectional, nationally representative sample of children participating in the National Health and Nutrition Examination Survey (NHANES) demonstrated enuresis in 8 % of children at 8 years, decreasing to 3 % at 11 years. Enuresis was more prevalent in boys than girls (6 vs. 2.5 %), with a 2.7-fold risk of enuresis among 8- to 11-year-old boys (OR2.69 [95 % CI 1.37–5.2]) (Shreeram et al. 2009).

Poly-symptomatic Enuresis

Prospective epidemiologic studies report daytime symptoms occurred in approximately 20–40 % of children with enuresis.

Of consecutive children referred to an enuresis clinic, daytime symptoms occurred in over 80 %.

The ALSPAC prospective cohort study of 13,973 children mentioned above described 1,260 (15.5 %) children with bedwetting (infrequent plus frequent), comprising mono-symptomatic enuresis in 12 %, and day and nighttime wetting in 3 %. Only 0.2 % experienced frequent (>2×/week) wetting episodes both during the day and night. Of children with nighttime wetting, 29 % had daytime urge symptoms, with increased likelihood with increasing frequency of enuresis (Butler et al. 2005).

In the cross-sectional epidemiological study reported by Yeung et al. (2006) above, daytime incontinence was present in 106 (21 %) of the 512 patients with bedwetting (>1×/3 months), including 38 (14 %) of 279 children aged 5–10 years and 68 (29 %) of 233 adolescents >10 years (Yeung et al. 2006).

Another cross-sectional study of 5,282 Japanese school children mean age 9 years (7–12) found bedwetting (>1×/month) in 6 %. Daytime symptoms, including frequency >8×/day and/or urge incontinence >1×/month, occurred in 41 % of these. The prevalence of poly-symptomatic enuresis was 3 % at age 7 years, and decreased to 0.8 % at age 12 years (Kajiwara et al. 2006).

An Australian cross-sectional study involved a random sample of 2,856 children from elementary schools with a mean age of 7.3 years (SD 1.3), reporting enuresis in 6 %. Daytime incontinence occurred in 17 %, associated with mild, moderate, and severe enuresis (1–6×/month; >7×/month but < nightly; 7×/week) in univariate analysis and multivariate logistic regression (adjusted OR [95 % CI]: 3.0 [2.1–4.2], 2.6 [1.3–5.2], and 4.8 [2.9–7.9]), respectively (Sureshkumar et al. 2009).

Among 170 patients with nocturnal enuresis (quantity not specified) enrolled into a prospective study of consecutive children aged ≥3.5 years presenting to a referral clinic for enuresis, 83 % experienced "urinary urgency" (not defined). Daytime wetting was present in 84 %, urinary frequency (>8×/day) in 39 %, and squatting maneuvers in 35 % of girls (Robson et al. 2005).

Secondary Enuresis

Approximately one-third of enuretics have onset after a dry period, comprising secondary enuresis.

One study found no difference in daytime symptoms in secondary versus primary enuretics.

Two studies reported life stressors such as divorce, birth of siblings, and school problems associated with secondary versus primary enuresis.

The prospective case–control study of 170 referred patients to an enuresis clinic mentioned above (Robson et al. 2005) reported primary enuresis in 123 (72 %) and secondary enuresis in 47 (28 %). Of the studied characteristics (demographic information, urologic history, uroflowmetry, and post-void residual), the only difference in those with secondary enuresis was the increased presence of constipation (diagnosed with palpable stool on abdominal exam and/or abdominal radiograph), in 75 % with primary versus 56 % with secondary enuresis (OR 2.17 [95 % CI 1.07–4.41]). Daytime symptoms, including incontinence, which was reported by 85 %, had similar frequency in both groups.

A prospective birth cohort study of 1,265 New Zealand children determined that the rate of nocturnal enuresis in 8-year-olds was 7 %, which the authors estimated represented secondary enuresis in one-third to one-half. Children exposed in any given year from ages 2–8 years to multiple life stressors, defined as change of parents or residence and/or other events from a 20-item Social Readjustment Rating Scale, were more likely to develop secondary enuresis (OR 2.56 [95 % CI 1.18–5.50]). This likelihood for secondary enuresis also related to age at which nighttime dryness was first achieved, with children not dry until age 5 years more susceptible than those dry at age ≤3 years (OR 3.39 [95 % CI 1.76–6.56]) (Fergusson et al. 1990).

A prospective study of 110 consecutive children with primary (82, 75 %) versus secondary (28, 25 %) enuresis that performed semi-structured child interviews and parental questionnaires found a higher rate of behavioral disorders (primarily internalizing) and/or life stressors (divorce, birth of sibling, school problems) in those with secondary enuresis (von Gontard et al. 1996).

Family History

One study of consecutive patients referred to a specialty enuresis clinic reported a positive family history in first- or second-degree relatives in 62 %.

A prospective cohort study found approximately 20 % of children with enuresis had a

parent with a history of bedwetting beyond age 5 years, equally affecting mothers and fathers.

Cross-sectional epidemiologic studies found increased likelihood for a child having enuresis if either mother or father reported bedwetting.

One study found sibling enuresis an independent risk factor compared to parental history.

Two twin studies report concordance in identical twins more than fraternal twins, suggesting a strong genetic component.

A prospective study evaluated family history among 167 consecutive children aged 5–10 years attending an outpatient enuresis clinic, of whom 110 had mono-symptomatic enuresis. A positive family history (parent, sibling, aunt, uncle, cousin) was reported by 67 (62 %), including 21 % of mothers, 23 % of fathers, and 17.5 % siblings (von Gontard et al. 1996).

A cross-sectional study of 3,206 Finnish 7-year-olds, of whom 8 % experienced bedwetting, found a positive family history in 37 %, with the risk of enuresis in a child 7.1 times greater (95 % CI 5.1–9.8) when the father had bedwetting beyond 4 years of age, and 5.2 times greater (95 % CI 3.9–7.0) when the mother did (Jarvelin et al. 1988).

Enuresis occurred in 159 (10 %) of 1,694 Turkish school children mean age 9 years (7–11 years) responding to a school-based cross-sectional survey. Univariate analysis found higher rates of parents and siblings with a history of treatment for enuresis among children with enuresis compared to those without enuresis (parental history: 68.5 vs. 4.6 %, $p<0.001$; sibling history: 34.6 vs. 2.3 %, $p<0.001$). Multiple logistic regression demonstrated that parental and sibling history of enuresis were both independent risk factors for enuresis (parent: OR 12.17, 95 % CI 4.05–36.61; sibling: OR 3.79, 95 % CI 1.23–11.68) (Inan et al. 2007).

In the ALSPAC prospective birth cohort study of 13,973 UK children mentioned above, detailed family history was obtained during the pregnancy of the enrolled child. Parents were asked if they experienced nighttime incontinence beyond the age of 5 years; a positive history was reported by 9 % of both mothers and fathers. Parent/child pairs were constructed based on frequency of bedwetting, and odds ratios were calculated to determine risk of enuresis. Rates of enuresis (>2 nights/week) at age 7.5 years were 3.63 and 1.85 times higher among children with a family history of maternal or paternal bedwetting, respectively (von Gontard et al. 2011a).

A prospective study in New Zealand followed children from birth to age 8 years, and obtained information regarding family history of enuresis from mothers of the children at the 5-year visit, recorded as number of first-degree relatives with nocturnal enuresis. The mean age of attaining bladder control ("regularly remained dry throughout the night") in children with zero, one, and two first-degree relatives with nocturnal enuresis were 3.7, 4.4, and 5.2 years, respectively ($p<0.0001$). On multivariate analysis, the number of first-degree relatives was the strongest predictor of age to attain bladder control, which on average occurred 1.5 years later when two first-degree relatives had nocturnal enuresis compared to those without a family history (Fergusson et al. 1986).

Among 338 pairs of twins prospectively enrolled in a study to evaluate "various behavior disorders," including bedwetting, thumb-sucking, and nail-biting, 146/676 (22 %) had enuresis, defined as wetting repeatedly >4 years of age. A positive history for a parent having had bedwetting was obtained in 85 %, equally involving mothers and fathers (Bakwin 1971).

Enuresis in the above-mentioned study reported that of the twins with enuresis, 68 % were monozygmatic versus 36 % dizygomatic, further supporting a strong genetic component (Bakwin 1971).

Similarly, a nationwide Finnish Twin Cohort of over 11,000 patients demonstrated a higher concordance rate of nocturnal enuresis in childhood among identical versus fraternal twins (43 vs. 19 %) (Hublin et al. 1998).

Associated Disorders

Constipation

Three prospective studies reported that encopresis, but not constipation, was a risk factor for nocturnal enuresis.

Two stated that fecal incontinence was associated with enuresis; it was found in 11 % of enuretics in one study.

The Australian cross-sectional study of 2,856 children described above categorized "severe" (nightly the past 1 month), "moderate" (≥7 episodes in past month), and "mild" (1–6 episodes the past month) enuresis. Constipation as defined by ROME-II criteria was not associated with mild, moderate, or severe enuresis (OR 0.7 [95 % CI 0.4–1.2], 1.5 [95 % CI 0.7–3.6], and 0.7 [95 % CI 0.3–1.9], respectively). However, encopresis was more likely with severe enuresis in multivariate logistic regression adjusting for age (OR 2.7 [95 % CI 1.6–4.4]), and marginally associated with mild and moderate enuresis (OR 1.6 [95 % CI 1.0–2.4] and 2.1 [95 % CI 1.1–4.3], respectively) (Sureshkumar et al. 2009).

The survey of Turkish school children reporting enuresis in 10 % mentioned above defined constipation as ≥2 of the following: bowel movement <3×/week, fecal incontinence >1×/week, palpable stools, stopping up toilet, withholding maneuvers, and/or pain with defecation. Univariable analysis reported both fecal incontinence and constipation more likely in enuretic versus non-enuretic children, but multivariate analysis demonstrated that only fecal incontinence, which occurred in 11 % with bedwetting, was an independent risk factor for enuresis (OR 6.13 [95 % CI 1.46–43.83]) (Inan et al. 2007).

The cross-sectional study of 5,282 Japanese school children reported above defined constipation as <3 bowel movements/week. There was no difference in rates of mono-symptomatic enuresis (6 %) in children with and without constipation, while poly-symptomatic urinary incontinence was more likely with constipation (3 % with vs. 2 % without, $p<0.05$) (Kajiwara et al. 2006).

A retrospective review of 30 consecutive patients mean age 9 years (5–15) with a "chief complaint of nocturnal enuresis" found 10 % reported constipation (bowel movement < every other day). Using a novel measurement of the ratio of the widest point of rectal diameter to pelvic outlet diameter on abdominal radiograph, all children had "fecal rectal distention" Therapy with polyethylene glycol for ≥2 weeks cured the enuresis in 25 (83 %) (Hodges and Anthony 2012). The number of wet nights/week before bowel therapy was not stated, and it was unclear if these patients had daytime incontinence. The indications for radiography and the number of other patients with enuresis not undergoing x-rays also were not stated.

Sleep-Disordered Breathing

A systematic review reported that approximately 33 % of children with sleep-disordered breathing (snoring, obstructive sleep apnea) also had enuresis.

Several population-based surveys report enuresis in 7–22 % of children who report sleep-disordered breathing, which is significantly greater than in children without snoring or sleep apnea (2–16 %).

Systematic review found tonsillectomy and adenoidectomy (T&A) reduced enuresis during median follow-up of 6 months.

A systematic review of 12 articles published from 1998 to 2010 included 3,550 children with sleep-disordered breathing, of which 1,113 (33 %) also had enuresis (not separated into primary versus secondary). Patient age ranged from 2 to 19 years. The authors commented that their finding that 33 % of patients age 6 years with sleep-disordered breathing also had enuresis suggests a relationship, given the usual prevalence of <15 % enuresis reported for this age. Seven articles with 1,360 patients (enuresis in 426, 31 %) had data regarding enuresis after T&A, finding that postoperative prevalence with median follow-up of 6 months was reduced to 16 % ($p=0.002$) (Jeyakumar et al. 2012).

Among 17,646 children aged 5–7 years in Kentucky completing a questionnaire about sleep habits, enuresis (defined as >2×/month) was present in 531/1976 (27 %) with habitual snoring (>3 nights/week and medium to loud on a loudness scale) versus 1,821/15,670 (12 %) without snoring ($p<0.00001$, OR 2.79 [95 % CI 2.50–3.13]). A random sample of 378 children at risk for sleep apnea based on these questionnaires underwent overnight polysomnography.

Of these, enuresis ≥3×/week was present in 33/149 (22 %) with obstructive sleep apnea and 36/229 (16 %) with habitual snoring but not obstructive sleep apnea. Severity of sleep disturbance did not correlate with severity of enuresis (Capdevila et al. 2008).

Two additional population-based cross-sectional studies also found increased rates of enuresis among children with snoring. Of 2,746 5–13-year-old children in Istanbul, children with occasional and habitual snoring had higher rates of nocturnal enuresis (quantity not specified) versus non-snorers (10 and 15 % vs. 7.5 %, $p=0.005$, OR 2.2 [95 % CI 1.2–3.5]) (Ersu et al. 2004).

Among 1,821 children aged 5–14 years in Greece, children with habitual snoring (>3 nights/week) were more likely to have primary nocturnal enuresis (>1×/week) versus non-snorers (7.4 vs. 2 %, OR = 4.00 [95 % CI 1.93–8.32]) (Alexopoulos et al. 2006).

A case–control study compared 149 children in a sleep-disorders clinic to 139 controls from general pediatric practice, and found that children with obstructive sleep apnea had higher odds of having mono-symptomatic enuresis (quantity not specified) (OR = 5.29 [95 % CI 2.25–12.45]) (Barone et al. 2009).

Another case–control study included 270 children referred to a sleep center for enuresis and 274 gender- and age-matched healthy children without enuresis as controls. Significant differences in sleep patterns occurred in enuretic versus healthy controls, as measured by the validated sleep disturbance scale for children (Carotenuto et al. 2011).

Attention Deficit/Hyperactivity Disorder

One literature survey reported a co-occurrence rate of attention deficit/hyperactivity disorder (ADHD)/behavioral problems and enuresis of 16–32 %.

One population-based US study found ADHD increased in children with enuresis (12 %), while a similar study of German children reported enuresis was not related to ADHD.

A literature survey concerned the co-occurrence of ADHD and enuresis in "recent studies" characterized as epidemiological ($n=6$) versus clinical ($n=12$), reporting ADHD/behavioral problems occurred in approximately 16–29 % of enuretics. Four other studies reported that enuresis occurred in 21–32 % of children with ADHD (Baeyens et al. 2005).

A population-based, nationally representative cross-sectional cohort of 1,136 US children found enuresis (defined by DSM-IV criteria and present within the past 12 months before the survey) in 4 % children aged 8–11 years. Using a validated structured diagnostic interview that elicits DSM-IV criteria for both enuresis and ADHD, nearly 10 % of children met DSM-IV criteria for ADHD. Enuretic children were more likely than non-enuretics to have ADHD: 12.5 vs. 4 % without, $p=0.001$. There was a 2.9-fold risk for ADHD among children with enuresis, OR 2.88 (95 % CI 1.26–6.57) (Shreeram et al. 2009).

The ALSPAC prospective birth cohort mentioned above demonstrated higher rates of parent-reported psychological problems, including attention problems, in children with any bedwetting and combined day and night wetting versus in those without wetting at age 7.5 years, bedwetting OR 1.58 (95 % CI 1.32–1.90), and combined wetting OR 2.23 (95 % CI 1.64–3.05) (Joinson et al. 2007).

Another cross-sectional study that controlled for developmental delay among a cohort of 1,379 children undergoing a mandatory school entry medical examination in Germany demonstrated that nocturnal enuresis alone was not a significant risk factor for symptoms of ADHD, whereas daytime incontinence with or without nocturnal enuresis strongly increased the odds of ADHD symptoms, OR 4.6 (95 % CI 1.6–13.0) (von Gontard et al. 2011b).

A cross-sectional study of 344 children enrolled in a genetic study of ADHD demonstrated a 17 % prevalence of enuresis (not quantified), which localized to the inattentive ADHD phenotype, but genome-wide analysis of 51 of these children did not identify an association with chromosomal regions previously linked to enuresis (Elia et al. 2009).

Psychologic Impact of Enuresis

One study reported children age 9 years considered bedwetting a social problem that ranked fourth of 21 difficult life events.

As noted earlier, behavioral problems are increased in children with both primary and secondary enuresis.

As part of the ALSPAC population-based study concerning health and development of children, questionnaires were sent to 10,985 children age 9 years, with 8,209 returns (75 % response) equally distributed between genders. They were asked to rate perceived difficulty of life events from a list of 21 items, as "not at all," "a little difficult," "quite difficult," and "really difficult." The top four most difficult events were "don't have friends," "being teased," "left out of things," and "wet the bed." Those rated less severe included "often ill," "move to a new school," "always in trouble," and "don't like how they look." Enuretic children (≥2 nights per week) comprised 1 % of respondents, and reported bedwetting a more difficult event than non-wetters. Nevertheless, 36 % of children dry at night rated bedwetting a "really difficult" problem. The fact that children rated bedwetting a more difficult problem than physical illness was interpreted by the authors to indicate that they perceive this a social, rather than medical, issue (Butler and Heron 2007).

Another ALSPAC questionnaire study concerned parental attitudes regarding combined bedwetting and daytime incontinence in children approximately 7.5 years old. Parents reported more psychological problems in children with combined wetting than those with only bedwetting or no wetting, as already mentioned in the section above (Joinson et al. 2007).

One-hundred ten consecutive children presenting to an enuresis clinic were diagnosed as having primary ($n=82$) or secondary bedwetting. Evaluation included a "full child psychiatric and psychological assessment," and parent questionnaires for life events they considered to have caused enuresis. Patients with secondary enuresis had significantly higher rates of behavioral disorders and psychological risk factors (such as divorce, sibling birth, entering kindergarten) (von Gontard et al. 1996).

Natural History

Spontaneous Resolution

Our review found no longitudinal study assessing spontaneous resolution rates of enuresis in a population of untreated children.

Short-term dryness (within 2–22 weeks) in nine RCTs was achieved in only 4 % of untreated controls.

No longitudinal study reports spontaneous resolution of bedwetting in untreated children.

The 15 % annual spontaneous resolution rate commonly quoted was derived from patients failing at least two drug treatments and behavioral modifications.

A questionnaire-based study of 1,129 (of 1,483) patients evaluated in an enuresis clinic in Belfast between 1952 and 1959 reported approximately 15 % "spontaneous" resolution per year in patients aged 5–19 years, with 33 (3 %) having continued enuresis after age 20 years (Forsythe and Redmond 1974). This study is frequently referenced in review articles of enuresis for the often-quoted 15 % rate of "spontaneous resolution" in children not treated with a bedwetting alarm. However, all these patients failed therapy with ≥2 drugs and many also failed various behavioral modifications, and so are not representative of untreated children. Furthermore, the numbers of patients evaluated at different ages to calculate annual resolution rates was not stated, and length of time of follow-up was not taken into account. Duration of time without wetting considered "cure" was not stated.

A Cochrane systematic review found no treatment or placebo arms of RCTs demonstrate <10 % of patients achieve 14 consecutive nights of dryness during the study periods (ranging from 2 to 22 weeks), and only 1–2 % remain dry. This pooled analysis of nine trials reporting data for bedwetting alarm versus no treatment reported

failure (<14 consecutive dry nights) in 250 of 260 (96 %) controls (Glazener et al. 2009a).

Our review did not find any long-term longitudinal cohort studies of enuretic patients reporting spontaneous resolution without medical, behavioral, and/or alarm therapy. Enuresis rates at various ages in population-based, cross-sectional studies such as those described provide prevalence rates at various ages, but it is unknown or not specified how many of these children received therapy to alleviate enuresis at any given point in time, and so these studies cannot be used to estimate true spontaneous resolution.

Evaluation

No laboratory, radiologic, or urodynamic testing is needed after history and physical examination in children with mono-symptomatic enuresis.

The following is a summary of current guidelines for evaluation of enuresis.

NICE guidelines (2010), derived from "best available evidence" by a team selected by the National Clinical Guidelines Centre, recommend the following:

- Urinalysis when there is a suspicion of diabetes or UTI, secondary enuresis, and/or daytime symptoms
- Voiding and fluid-intake diaries
- No radiographic studies

European Association of Urology guidelines, derived primarily from expert consensus, recommend the following:

- Diagnosis is made by history alone without further investigation for mono-symptomatic enuresis (Tekgul et al. 2009).

ICCS guidelines, derived from "what evidence there is" (described as weak) and expert consensus, recommend the following:

- Urinalysis to evaluate glycosuria and/or proteinuria
- No renal ultrasound
- A 2-day chart of urinary frequency/volume and fluid volume consumed
- A 1-week chart of enuresis, daytime incontinence, and bowel movements (Neveus et al. 2010).

Treatment

Behavioral Interventions (Random Awakening, Fluid Restrictions, Rewards)

Cochrane review of RCTs reported wakening not triggered by a wetting episode was not effective therapy for enuresis.

Cochrane review of behavioral and educational interventions for enuresis, including wakening not triggered by a wetting episode, as well as night-time fluid restriction and reward systems, analyzed 18 trials involving 1,174 children. Behavioral interventions alone were not as effective as alarms alone or alarms plus behavioral therapy, with RR for failure or relapse with behavioral intervention versus alarm plus intervention 2.81 (95 % CI 1.80–4.38) (Glazener et al. 2008).

Alarm Conditioning

Cochrane review reported alarm use for 2–22 weeks resulted in 14 consecutive dry nights in 50–75 % of children. Approximately 50 % of children remained dry after active treatment.

A more rapid response may be achieved using medication, but overall effectiveness during therapy was considered similar by Cochrane review.

Relapse rates were less after alarm therapy versus medication.

Cochrane review of 56 RCTs involved 3,257 children, 2,412 of whom used an alarm. Duration of treatment varied but ranged from 2 to 8 weeks in 16 trials, up to more than 12 weeks in 22 trials. Only 29/56 (52 %) studies provided follow-up data to determine relapse rates. Here is a summary of key findings:

- Alarm versus no treatment: About two-thirds of patients using alarms became dry (RR for failure 0.38 [95 % CI 0.33–0.45]), and about half failed or relapsed after alarm conditioning, while nearly all controls remained wet.

- Alarm versus placebo: Alarms were better than placebo for fewer wet nights during and after treatment.
- Alarm versus desmopressin: Desmopressin may achieve dryness faster than alarm, although there appear to be no differences during an entire treatment course, RR 0.85 (95 % CI 0.53–1.37). In two small trials, relapse was less after alarm therapy (26/57 [46 %] vs. 40/62 [65 %]).
- Alarm versus tricyclics: There was no difference in response during treatment, RR 0.59 (95 % CI 0.32–1.09), but alarms had lower relapse rates after treatment, RR 0.58 (95 % CI 0.36–0.94).
- Alarm plus desmopressin: there was no difference in treatment success in alarm versus alarm plus desmopressin trials.

There were no clear-cut differences noted in types of alarms (body vs. pad), although two small trials demonstrated fewer wet nights among alarms with immediate wakening versus time delay of 3 min (Glazener et al. 2009a).

Desmopressin

Cochrane meta-analysis reported that desmopressin achieved 14 consecutive dry nights in approximately 20 % of children versus 2 % of controls.

One trial increased desmopressin dosing at 2-week intervals, reporting progressively decreased wet nights with increasing dose to 0.6 mg, but only 8 % of treated children became dry.

Relapse after therapy is similar in children treated with desmopressin and those receiving no medication.

One RCT reported desmopressin plus tolterodine achieved >50 % reduction in wet nights during 1 month of therapy in patients with enuresis failing desmopressin alone.

Cochrane review included 47 RCTs involving 3,448 children, with 2,210 receiving desmopressin. All but 10 of these studies involved the intranasal route (no longer available), with the remaining using oral tablets. Sample sizes of these studies ranged from 10 to 182 patients (mean 73) and were conducted for various lengths of time at varying dosing regimens. Key summarized findings included the following:

- Desmopressin versus placebo: At an intranasal dose of 20 μg, pooled data demonstrated a mean of 1.34 fewer wet nights per week (95 % CI 1.11–1.57). Doses of 40 μg and 60 μg decreased the number of wet nights per week by 1.33 and 1.50 nights/week, respectively (95 % CI 1.67–0.99 and 1.92–1.08). Nineteen percent of treated children became dry versus 2 % of controls. Four trials suggested results were not sustained after treatment ended.
- Desmopressin versus tricyclics: More children in two trials became dry with desmopressin during treatment, RR for failure to achieve 14 consecutive dry nights 0.44 (95 % CI 0.27–0.73), but there were no data regarding relapse after therapy.
- Desmopressin versus alarms: See section above.
- Adverse Events: All reported events were minor and did not result in stopping treatment. There is a risk for water intoxication, which is minimized by fluid restriction before bedtime (Glazener and Evans 2009).

In one multicenter dose-escalation study, 148 children (ages 6–16 years, 73 % males, average 10–11 wet nights per 2 weeks) were assigned to placebo or desmopressin beginning at 0.2 mg at bedtime for 2 weeks, and then increased every 2 weeks at 0.2-mg increments until either dry or receiving a maximum 0.6 mg. There was a significant linear decrease in wet nights from baseline a mean of 10, 27, 30, and 40 % for placebo, 0.2, 0.4, and 0.6 mg desmopressin. A 50 % reduction in wetting from baseline occurred in 28 % of patients at 0.2 mg, 16 % at 0.4 mg, and 9 % at 0.6 mg. However, only 11/141 (8 %) desmopressin patients became dry versus 0/47 receiving placebo (Schulman et al. 2001).

One RCT enrolled 34 nonresponders or partial responders to desmopressin with mono-symptomatic enuresis (mean age 10.5 years, 70 % males) to desmopressin plus 4 mg tolterodine versus desmopressin plus placebo for 1 month. Treatment outcomes were described as either success (>50 % reduction in wet nights) or no success. Success was achieved significantly more

with desmopressin plus tolterodine, 8/18 (44 %) versus desmopressin plus placebo 5/16 (31 %) (Austin et al. 2008).

FDA Adverse Events Reporting

Desmopressin in combination with excessive fluid intake can result in hyponatremia, which can lead to brain swelling, seizure, and, rarely, death. However, no RCTs involving its use for bedwetting reported these events during the study period. In 2007, the FDA indicated post-marketing reports of 61 seizures among users of desmopressin nasal spray to treat various medical conditions. Thirty-one of these patients had other concomitant medicines/diseases associated with hyponatremia and/or seizures. Nevertheless, the FDA recommended against intranasal administration for the treatment of primary nocturnal enuresis in children.

Imipramine

Cochrane review found that imipramine was more effective than placebo for enuresis, with approximately 20–33 % achieving 14 consecutive dry nights during therapy.

Relapse occurred in approximately 66 % of patients when treatment stopped at 3 months.

Cochrane review included 58 RCTs involving 3,721 children. Results were pooled for the various tricyclics, which was primarily imipramine but also included desipramine, amitriptyline, nortriptyline, viloxazine, trimipramine, mianserin, and clomipramine. Study sample sizes were generally small. Various dosing regimens and lengths of treatment were used. Key findings included the following:

- Tricyclics versus placebo: There were fewer wet nights for patients receiving tricylics versus controls. Meta-analysis was possible using data from only three trials, finding an average of one fewer wet night per week, −0.92 (95 % CI −1.38 to −0.46). Eleven trials found 21 % of treated children achieved 14 consecutive dry nights, versus 5 % on placebo, RR for failure 0.77 (95 % CI 0.72–0.83). After stopping therapy, only 4 % who took imipramine versus 3 % who took placebo remained dry.
- Dose-related efficacy: Two trials compared higher versus lower dose imipramine, with one reporting there was no difference (but not providing data), while the other showed one fewer wet night per week at 25 mg compared to 10 mg.
- Tricyclics versus desmopressin: See section above.
- Tricyclics versus alarm: See above.

Adverse Events

Twenty-nine trials provided some information regarding side effects, but no major adverse events, specifically arrhythmia or heart block, occurred (Glazener et al. 2009b).

Oxybutynin

Oxybutynin monotherapy is no more effective than placebo for enuresis.

NICE guidelines pooled results demonstrated no difference in patients receiving oxybutynin versus placebo to achieve either >90 % (6/16 [37.5 %] vs. 5/23 [21.7 %], RR 1.73 [95 % CI 0.63–4.69]), or 50–90 % dry nights (6/15 [37.5 %] vs. 8/23 [4.8 %] RR 1.08 [5 % CI 0.46–2.51]) (NICE 2010).

A crossover double-blinded RCT of 30 children (mean age 10 years, 83 % boys, some previously treated with imipramine) with primary nocturnal enuresis assigned to placebo versus oxybutinin 5 mg nightly for 4 weeks demonstrated no difference in the number of dry nights. There was a mean decrease in wetting of 1.9 nights/week (Lovering et al. 1988).

Alternative Therapies: Acupuncture, Hypnosis, Psychotherapy, Chiropractor Adjustment, Homeopathy

No alternative therapy listed here has been found effective for enuresis treatment.

A 2011 update regarding complementary and miscellaneous interventions for enuresis was performed by the Cochrane Incontinence Group. Several small, poor-quality trials provide weak

evidence in support of hyponosis, psychotherapy, acupuncture, chiropractic, and medicinal herbs (Huang et al. 2011).

Order of Therapy

Synthesizing outcomes data and cost analysis, NICE guidelines recommended, in descending order, the following:

- Alarm as first-line therapy
- Alarm plus desmopressin or desmopressin alone if alarm is ineffective
- Desmopressin plus anticholinergic
- Imipramine

Impact of Therapy on Self-Esteem

One study of enuretics versus matched controls using non-validated instruments to determine personality attributes and behavioral problems reported that parent and therapist assessment, but not that by teachers, improved with successful alarm therapy.

Subsequent trials using validated instruments found parent-rated behavior improved in patients regardless of treatment outcomes.

Two trials concluded that successful treatment of enuresis did not impact psychological health of the child, although another reported significant improvement in self-concept. One trial using imipramine found improved behavior that correlated with decreased wetting, but could not determine if the changes were secondary to therapeutic success versus euphoric effects of the medication.

A study of 30 enuretic children and 60 gender- and age-matched controls assessed personality characteristics and behavioral problems. Median age was 8 years (6–12), 20 boys, and enuresis occurred nightly in "more than half." Of the 30 with bedwetting, 10 were treated with alarms, 10 with scheduled night wakening, and 10 were not treated. Parents completed (non-validated) rating scales to assess personality attributes (confidence, anxiety) and behavioral problems (such as tantrums, thumb-sucking) before and "several weeks" after treatment. Their teachers used a different rating scale modified for the study and filled out just before treatment, 10 weeks later (end of treatment), and another 3 months later. The enuretic children and 30 of the controls were also tested by a psychologist using a novel "self-image questionnaire" created for the study and a "neurotic inventory" previously reported in another study of enuretics. There was no difference in patients versus controls on any pretreatment test. Parent ratings after treatment were significantly better in patients who stopped wetting. Teacher scores did not change regardless of response to therapy. Therapist ratings were improved in patients who stopped wetting, significantly different than the "improvement" during the same time in controls. No children who stopped wetting had worsening in adjustment symptoms, but rather were reported to be happier and less anxious (Baker 1969).

A subsequent study used similar methods but included more patients, used validated assessment instruments, and had longer follow-up to 1 year after treatment. There were 83 enuretic children (male to female ratio 3:1) who had been referred at median age 9 years to a child guidance center because of their bedwetting who were treated either with alarm ($n=64$), psychotherapy/counseling ($n=10$), or no treatment ($n=9$), and of these 51, 2, and 2, respectively, had success (13 consecutive dry nights). Mothers completed a behavioral questionnaire, the children a personality assessment, and their teachers a different behavioral rating before and 1, 6, and 12 months after treatment. There was no difference in the three groups in pretreatment or at 1 month posttreatment ratings. All three showed a decrease in mother-reported behavioral problems at 1 month post treatment, which the authors concluded represented either placebo effect (change in parental perception because of clinic contacts) or the result of repeat testing, but was not due specifically to enuresis therapy. Similarly, 6- and 12-month data showed patients successfully treated continued to have decreased mother-reported ratings, but so did those not achieving "cure." Consequently, there was no evidence that enuresis treatment impacted psychological health (Sacks et al. 1974).

A RCT enrolled children with enuresis and allocated them to alarm ($n=66$) or no treatment ($n=55$, "waiting list"). Treatment continued until patients had 14 consecutive dry nights, and then "overlearning" was done, having them drink additional fluids at bedtime with alarm use continued until there was another 14 consecutive dry nights. Validated self-concept and behavioral questionnaires were rated by children and parents at baseline and after treatment. Parent-rated behavior improved in both groups without difference. Significant self-concept improvement occurred in the treated patients (Moffatt et al. 1987).

Another trial recruited subjects from local pediatric clinics and by advertisements that attracted 148 children, from which a total of 40 were enrolled on the basis of several inclusion criteria. These were randomized to alarm, imipramine, or no treatment ("waiting list"), with treatment continued until the child was dry for 14 consecutive nights or for 14 weeks. Behavioral health and emotional health were determined by child and parent ratings on validated instruments before and after treatment. There were no significant behavioral or emotional effects from treatment. Despite different success rates, there was no difference in post-treatment psychological assessments in patients using alarms versus imipramine (Wagner et al. 1982).

While imipramine is used to stop enuresis, the fact that most enuretics have no psychiatric defect raised questions regarding effects of an antidepressant medication in psychologically normal children. A double-blinded, placebo-controlled crossover study was designed using 50 mg imipramine for 3 weeks in boys recruited by a newspaper story. There were 21 completers. Imipramine effects included significant but small increases in resting heart rate (placebo 82 vs. 98) and diastolic blood pressure (placebo 65 vs. 73). There was nonsignificant improvement in cognitive performance on imipramine. A low but significant correlation was found between changes in wetting and behavior, but it was not possible to determine if this was due to decreased wetting or any euphoric effect of imipramine. The authors concluded imipramine has similar psychotropic effects to stimulants, such as those used for hyperactivity (Werry et al. 1975).

References

Alexopoulos EI, Kostadima E, Pagonari I, Zintzaras E, Gourgoulianis K, Kaditis AG. Association between primary nocturnal enuresis and habitual snoring in children. Urology. 2006;68(2):406–9.

Austin PF, Ferguson G, Yan Y, Campigotto MJ, Royer ME, Coplen DE. Combination therapy with desmopressin and an anticholinergic medication for nonresponders to desmopressin for monosymptomatic nocturnal enuresis: a randomized, double-blind, placebo-controlled trial. Pediatrics. 2008;122(5):1027–32.

Baeyens D, Roeyers H, Demeyere I, Verte S, Hoebeke P, Vande WJ. Attention-deficit/hyperactivity disorder (ADHD) as a risk factor for persistent nocturnal enuresis in children: a two-year follow-up study. Acta Paediatr. 2005;94(11):1619–25.

Baker BL. Symptom treatment and symptom substitution in enuresis. J Abnorm Psychol. 1969;74(1):42–9.

Bakwin H. Enuresis in twins. Am J Dis Child. 1971;121(3): 222–5.

Barone JG, Hanson C, DaJusta DG, Gioia K, England SJ, Schneider D. Nocturnal enuresis and overweight are associated with obstructive sleep apnea. Pediatrics. 2009;124(1):e53–9.

Butler RJ, Golding J, Northstone K. Nocturnal enuresis at 7.5 years old: prevalence and analysis of clinical signs. BJU Int. 2005;96(3):404–10.

Butler R, Heron J. An exploration of children's views of bed-wetting at 9 years. Child Care Health Dev. 2007;34(1):65–70.

Butler RJ, Heron J. The prevalence of infrequent bedwetting and nocturnal enuresis in childhood. A large British cohort. Scand J Urol Nephrol. 2008;42(3): 257–64.

Capdevila OS, Kheirandish-Gozal L, Dayyat E, Gozal D. Pediatric obstructive sleep apnea: complications, management, and long-term outcomes. Proc Am Thorac Soc. 2008;5(2):274–82.

Carotenuto M, Esposito M, Pascotto A. Facial patterns and primary nocturnal enuresis in children. Sleep Breath. 2011;15(2):221–7.

Elia J, Takeda T, Deberardinis R, Burke J, Accardo J, Ambrosini PJ, et al. Nocturnal enuresis: a suggestive endophenotype marker for a subgroup of inattentive attention-deficit/hyperactivity disorder. J Pediatr. 2009;155(2):239–44. e5.

Ersu R, Arman AR, Save D, Karadag B, Karakoc F, Berkem M, et al. Prevalence of snoring and symptoms of sleep-disordered breathing in primary school children in istanbul. Chest. 2004;126(1):19–24.

Fergusson DM, Horwood LJ, Shannon FT. Factors related to the age of attainment of nocturnal bladder control: an 8-year longitudinal study. Pediatrics. 1986;78(5): 884–90.

Fergusson DM, Horwood LJ, Shannon FT. Secondary enuresis in a birth cohort of New Zealand children. Paediatr Perinat Epidemiol. 1990;4(1):53–63.

Forsythe WI, Redmond A. Enuresis and spontaneous cure rate. Study of 1129 enuretis. Arch Dis Child. 1974;49(4): 259–63.

Glazener C, Evans J, Peto RE. Complex behavioural and educational interventions for bedwetting (nocturnal enuresis) in children. Cochrane Database Syst Rev. 2008. Art. No.: CD004668. doi: 10.1002/14651858. CD004668.

Glazener C, Evans J, Peto RE. Alarm interventions for nocturnal enuresis in children. Cochrane Database Syst Rev. 2009. Art No. CD002911. doi: 10.1002/14651858. CD002911.

Glazener C, Evans J, Peto RE. Tricyclic and related drugs for nocturnal enuresis in children. Cochrane Database Syst Rev. 2009b. Art No. CD002117. doi: 10.1002/14651858. CD002117.

Glazener CM, Evans JH. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev. 2009. Art No. CD002112. doi: 10.1002/14651858. CD002112.

Hodges SJ, Anthony EY. Occult megarectum–a commonly unrecognized cause of enuresis. Urology. 2012;79(2):421–4.

Huang T, Shu X, Huang YS, Cheuk DK. Complementary and miscellaneous interventions for nocturnal enuresis in children. Cochrane Database Syst Rev. 2011;(12): CD005230.

Hublin C, Kaprio J, Partinen M, Koskenvuo M. Nocturnal enuresis in a nationwide twin cohort. Sleep. 1998;21(6): 579–85.

Inan M, Aydiner CY, Tokuc B, Aksu B, Ayvaz S, Ayhan S, et al. Factors associated with childhood constipation. J Paediatr Child Health. 2007;43(10):700–6.

Jarvelin MR, Vikevainen-Tervonen L, Moilanen I, Huttunen NP. Enuresis in seven-year-old children. Acta Paediatr Scand. 1988;77(1):148–53.

Jeyakumar A, Rahman SI, Armbrecht ES, Mitchell R. The association between sleep-disordered breathing and enuresis in children. Laryngoscope. 2012;122(8): 1873–7.

Joinson C, Heron J, Emond A, Butler R. Psychological problems in children with bedwetting and combined (day and night) wetting: a UK population-based study. J Pediatr Psychol. 2007;32(5):605–16.

Kajiwara M, Inoue K, Kato M, Usui A, Kurihara M, Usui T. Nocturnal enuresis and overactive bladder in children: an epidemiological study. Int J Urol. 2006; 13(1):36–41.

Lovering JS, Tallett SE, McKendry JB. Oxybutynin efficacy in the treatment of primary enuresis. Pediatrics. 1988;82(1):104–6.

Moffatt ME, Kato C, Pless IB. Improvements in self-concept after treatment of nocturnal enuresis: randomized controlled trial. J Pediatr. 1987;110(4):647–52.

Neveus T, Eggert P, Evans J, Macedo A, Rittig S, Tekgul S, et al. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol. 2010;183(2):441–7.

NICE (National Institute for Clinical Excellence). Nocturnal enuresis—the management of bedwetting in children and young people. Clinical guidelines, CG111. Issued: October 2010.

Robson WL, Leung AK, Van Howe R. Primary and secondary nocturnal enuresis: similarities in presentation. Pediatrics. 2005;115(4):956–9.

Sacks S, De Leon G, Blackman S. Psychological changes associated with conditioning functional enuresis. J Clin Psychol. 1974;30(3):271–6.

Schulman SL, Stokes A, Salzman PM. The efficacy and safety of oral desmopressin in children with primary nocturnal enuresis. J Urol. 2001;166(6):2427–31.

Shreeram S, He JP, Kalaydjian A, Brothers S, Merikangas KR. Prevalence of enuresis and its association with attention-deficit/hyperactivity disorder among U.S. children: results from a nationally representative study. J Am Acad Child Adolesc Psychiatry. 2009;48(1): 35–41.

Sureshkumar P, Jones M, Cumming R, Craig J. A population based study of 2,856 school-age children with urinary incontinence. J Urol. 2009;181(2):808–15. discussion 15–6.

Tekgul S, Riedmiller H, Gerharz E, Hoebeke P, Kokvara R, Nijman R, et al. Monosymptomatic enuresis. Guidelines on pediatric urology. Arnhem, The Netherlands: European Association of Urology; 2009. p. 29–31.

von Gontard A, Hollmann E, Eiberg H, Benden B, Rittig S, Lehmkuhl G. Clinical enuresis phenotypes in familial nocturnal enuresis. Scand J Urol Nephrol. 1996;183: 11–6.

von Gontard A, Heron J, Joinson C. Family history of nocturnal enuresis and urinary incontinence: results from a large epidemiological study. J Urol. 2011a;185(6):2303–6.

von Gontard A, Moritz AM, Thome-Granz S, Freitag C. Association of attention deficit and elimination disorders at school entry: a population based study. J Urol. 2011b;186(5):2027–32.

Wagner W, Johnson SB, Walker D, Carter R, Wittner J. A controlled comparison of two treatments for nocturnal enuresis. J Pediatr. 1982;101(2):302–7.

Werry JS, Dowrick PW, Lampen EL, Vamos MJ. Imipramine in enuresis–psychological and physiological effects. J Child Psychol Psychiatry. 1975;16(4): 289–99.

Yeung CK, Sreedhar B, Sihoe JD, Sit FK, Lau J. Differences in characteristics of nocturnal enuresis between children and adolescents: a critical appraisal from a large epidemiological study. BJU Int. 2006;97(5):1069–73.