Clinical Perspectives in Primary Nocturnal Enuresis

Gretchen A. Gimpel, PhD
William J. Warzak, PhD
Brett R. Kuhn, PhD
John N. Walburn, MD

Summary: Primary nocturnal enuresis (PNE) is prevalent among the pediatric population, but not all professionals are aware of the current research regarding the etiology and treatment of this disorder. This paper presents a broad overview of PNE, including etiology and evaluation, with a specific emphasis on treatment issues. The most current treatments (imipramine, desmopressin acetate arginine vasopressin, enuresis alarms) are discussed, including recent research on their effectiveness. In considering the recent data on long-term efficacy, overall cost, and safety, the treatment of choice appears to be the enuresis alarm for those families who are capable of following protocols. Desmopressin acetate arginine vasopressin is a safe alternative that has the advantage of quick response and ease of administration. Clin Pediatr. 1998;37:23-30

Introduction

Nocturnal enuresis affects 15% to 20% of 5-year-old children, with an estimated five to seven million American children over the age of 5 experiencing primary nocturnal enuresis (PNE). The diagnosis is typically reserved for children who wet more than twice a month and who have no significant physiologic or additional general medical conditions. Given the prevalence of this disorder, it is important that pediatricians have an understanding of its etiology and treatment. The purpose of this paper is to briefly review the empirical literature on PNE, including recent treatment outcomes, findings for imipramine, desmopressin, and enuresis alarms. Medical evaluation for PNE and the risks and benefits of the available treatment options are presented for the pediatric care provider.

Etiology

It seems most probable that various etiologic factors contribute to PNE. Organic and structural factors affect as few as 1–3% of PNE patients, while familial factors have a strong association. The incidence of PNE is 77% among children who have both a mother and a father with a history of PNE. This rate decreases to 44% in children who have just one parent with a history of PNE and to 15% in children who have no parental history of PNE. Indices such as height, bone growth, and Tanner scores have been found to be less developed in children with PNE relative to their nonwetting peers, suggesting that maturational and developmental factors may also be relevant to PNE.

Sleep factors have also been investigated although current research is inconclusive regarding the link between sleep and enuresis. In a recent survey, 60% of par-
When children enuretic are evaluated by professionals, the parents of children with PNE report their children were likely to awaken as compared with those children without PNE.  

Recently, increased nocturnal urine output due to insufficient nocturnal production of antidiuretic hormone (ADH), impaired renal sensitivity to arginine vasopressin and desmopressin, has been implicated in the etiology of PNE. This view, though, does not account for diurnal enuretic episodes that occur during naptime in uncomplicated patients with PNE, nor does it explain why a child fails to awaken to the stimulus of a full bladder.

Finally, behavioral factors have been considered contributory. Although PNE is not typically the result of behavioral pathology, PNE may contribute to behavioral difficulties for children. Almost two thirds of parents of children with PNE report that bed wetting is a significant problem and one third report frequently dealing with bed wetting through punishment. Children who present for treatment are often under more stress and have more behavioral symptoms than children whose parents do not seek treatment.

**Evaluation**

Because of the large numbers of enuretic children and the spontaneous remission rate of approximately 15% a year, treatment is often deferred until age 6 or 7. Children of this age who still experience regular enuretic episodes should be considered for evaluation. However, even younger children whose parents seek professional help are candidates for intervention. Many children experience an increase in self-esteem following successful treatment, providing a good rationale for treating these patients.

All children with PNE should be screened by a physician for evidence of organic or structural problems. The initial evaluation should include a complete medical history in which the child’s health history, family history, and psychosocial variables are assessed. It is important to identify any history of urinary or gastrointestinal problems, such as concurrent stool incontinence or constipation. Significant constipation, sometimes associated with diurnal enuresis, should be addressed before any treatment for enuresis is begun. The physical examination is performed to ensure that the neurophysiology of the bladder is normal, including the abdominal, cremasteric, anal, and deep tendon reflexes. Musculoskeletal abnormalities such as “claw feet” or abnormal gait might indicate developmental abnormalities of the spinal cord, such as tethered cord. The examination should include looking for a deep pilonidal dimple, particularly one associated with a patch of hair, that might suggest spinal cord abnormalities. An evaluation of the child’s abdominal and genital areas, and observation of the child voiding if an abnormal stream is reported by history, should also be part of the physical examination. A urinalysis and urine culture will rule out urinary tract infections and may screen for renal or metabolic disorders, such as diabetes mellitus or diabetes insipidus, that may be contributory. Finally, normal bladder capacity for children up to 11 years of age may be estimated by the formula: age (years old) + 2 = bladder capacity (in ounces). If any of these evaluations yields signs of dysfunction, further assessment is warranted.

**Treatment**

Treatment of PNE typically involves behavioral or pharmacologic interventions. The bed-wetting alarm, often used in conjunction with other behavioral procedures such as self-monitoring and positive reinforcement, is the most well-researched behavioral intervention. The most frequently used pharmacologic treatments for PNE are imipramine (Tofranil®) and desmopressin (DDAVP). Differences in outcome criteria make comparisons across medication and alarm studies difficult. Researchers of alarm interventions most commonly report the percentage of children who completely stop wetting for a specified period of time (often 14 consecutive nights), whereas researchers of pharmacologic interventions are more likely to report results as a reduction in wet nights compared with pretreatment observation. Nevertheless, children who receive either behavioral or pharmacologic treatment are significantly more likely to stop wetting the bed than children who receive no treatment or a placebo.

**Imipramine**

Imipramine, a tricyclic antidepressant first used in the treatment of PNE in the 1960s, is one of the most commonly prescribed medications for the treatment of...
Primary Nocturnal Enuresis

bed wetting. Recent reviews of the literature have identified four hypotheses regarding its mechanisms of action: antidepressant effects, changes in sleep and arousal, anticholinergic effects, and stimulation of antidiuretic hormone production. The first three hypotheses have received little support in the recent literature. The last hypothesis seems promising, but further research is needed.

Unfortunately, imipramine does not seem to have lasting effects for the majority of children who take it. Once imipramine is discontinued, it is likely that the child will resume wetting the bed, especially if medication is discontinued abruptly without tapering. Studies examining the effectiveness of imipramine report relapse rates ranging from 60% to 95% following discontinuation of the medication.

Typical dosages of imipramine for PNE are 25 mg nightly for children ages 6–8 and 50–75 mg nightly for older children and adolescents. Based on weight, a dose of 0.9 to 1.5 mg/kg is typical. Recent research suggests that larger doses of imipramine result in more effective treatment of PNE, but the therapeutic window of clinical efficacy is narrow, emphasizing the importance of close monitoring. Tracking serum concentrations may be helpful in determining a clinically effective dosage. Doses greater than 2.5 mg/kg per day (to a maximum of 75 mg per day) should not be prescribed for PNE, and alternative therapies should be considered once doses approach that level without significant effect.

Children treated with imipramine often continue the medication for 3 to 6 months, but an optimal length of treatment has yet to be identified. A recent review found that the longer children were treated with tricyclics, the less likely they were to become dry, suggesting that extended treatment with imipramine may not necessarily increase the therapeutic benefit or produce lasting effects.

Among imipramine, desmopressin, and alarm therapies, imipramine therapy is associated with the greatest risk for adverse reactions. Although the low doses of imipramine commonly used to treat bed wetting have relatively few serious side effects, adverse reactions have been documented in some patients. Irritability, reduced appetite, dry mouth, and headaches have been reported, as have significant increases in heart rate. An EKG may not identify children at risk for cardiac complications, and a negative result does not preclude future complications as a function of this therapy. More serious side effects (i.e., CNS and cardiac toxicities) may occur in some patients. One case study reported liver failure in a boy treated for PNE with 25 mg of imipramine per day. Accidental poisonings have also occurred, most often in the United Kingdom, where imipramine is the most common cause of fatal poisonings in children under 5 years of age. It is critical for pediatric care providers to inform parents of the potential adverse effects of imipramine, to supervise administration, to store medication in child-proof containers, and to place the medication out of the reach of younger children.

Desmopressin

Desmopressin acetate (DDAVP) is another commonly used medication in the treatment of PNE. DDAVP is a synthetic analog of arginine vasopressin, an antidiuretic hormone. Desmopressin acts at the distal tubules of the kidneys to increase water reabsorption in the collecting duct, resulting in a low volume of urine with high osmolality. DDAVP was originally formulated as a nasal spray, but a tablet form has recently become available. The tablet has pharmacokinetics similar to that of the intranasal spray, but its bioavailability differs, 10% bioavailability resulting from the intranasal preparation and less than 1% from the oral preparation. DDAVP is often successful in decreasing the number of wet nights a child experiences, but dryness may not be maintained upon discontinuation of treatment. The percentage of children who remain dry 6 to 12 months following termination of intranasal DDAVP ranges from approximately 5% to 21% in some studies. Reported relapse rates have ranged from approximately 50 to 95%, but dryness may not be maintained upon discontinuation of treatment. The percentage of children who remain dry 6 to 12 months following discontinuation of DDAVP, consistent with the annual spontaneous remission rate.

DDAVP dosage is not titrated by patient weight. It is commonly given in doses of 20 or 40 µg (intranasal spray) and 200 or 400 µg (oral preparation). There are conflicting reports regarding the optimal dose, and this may vary according to the individual child. One review suggested 40 µg as the most common optimal dose of the intranasal preparation, although another study found DDAVP to be effective in some children with doses at 10 µg and less. Recent studies with the oral preparation have reported greater effectiveness with the higher dose. DDAVP should be administered 30 to 60 minutes prior to bedtime to maximize effectiveness. Fluid intake should...
be restricted on the evenings it is taken to avoid hyponatremia, as noted in the manufacturer’s insert. No optimal length of time for a child to remain on DDAVP has been identified. Investigations have varied from 1 or 2 weeks to several months.

In general, the side effects of DDAVP are mild, with epistaxis, nasal discomfort, headaches, and abdominal pain among the most commonly reported.66 Seizures secondary to hyponatremia are rare, and it would appear that many of these patients had consumed excessive fluids relative to the manufacturer’s instructions, with resulting water intoxication and low serum sodium resulting from the antidiuretic action of desmopressin.67 Cystic fibrosis may also contribute to complications with DDAVP therapy. Other patients may be excessively sensitive to desmopressin at the recommended doses. Nevertheless, an LD50 has not been established and doses as high as 20,000 times the recommended clinical dose have been given to laboratory animals with only minor and transient effects, such as diminished coordination and decreased motor activity.68 No patient deaths have been associated with desmopressin.

**Enuresis Alarm**

The bed-wetting alarm was first developed in 1938.69 Today’s alarms are more compact than the original ‘bell and pad’ and most often consist of a small alarm box worn on the wrist or shoulder with wires attaching the alarm box to snaps separated by the child’s sleep garment. The moisture (or salts) of the child’s urine completes the circuit, causing the alarm to sound or vibrate and awaken the child. It has been proposed that the alarm works through classical conditioning and that through repeated pairings of a full bladder, the child wetting, the alarm sounding, and the child waking, the child learns to wake to the sensation of a full bladder prior to voiding. Children may also perceive the alarm, waking in the night, and clean up, as an aversive condition and learn to avoid this by learning to be dry.49

The enuresis alarm may be the most effective treatment for PNE, with estimated success ranging up to 70%,50 but the alarm must be used consistently and appropriately or children will have little chance of achieving dryness. The main disadvantage of the alarm is that it takes a great deal of patient effort and motivation. Children must wake up when the alarm sounds and follow specified procedures. Children frequently do not awaken when first using the enuresis alarm, and it is imperative for a family member to wake the child immediately if he or she does not awaken independently. Once fully awake, the child should disconnect the alarm and attempt to void in the toilet. The alarm should then be reattached. Children for whom the alarm is effective generally become dry within 2–4 months. Although some children may relapse and begin wetting again after discontinuing the alarm, immediate reimplementation of the alarm often corrects this relapse in a short period of time.51 A proposed drawback of the alarm, that it disrupts children’s sleep schedules even once they are dry, has not been supported by recent studies.52,53 Success can be enhanced by making patients and parents aware of the time required for this procedure to be successful. Disorganized or dysfunctional families, including families in which the child may be at risk for abuse, are not good candidates for an alarm regimen. Neither are children who present with an urgent need to be dry, perhaps for an overnight or summer camp. Once continence has been attained, relapses may be addressed by reintroducing the alarm, usually with more rapid success than was experienced during initial treatment.

In one study using enuresis alarms and dry bed training, 36.1% of the children had relapsed (defined as two or more wet nights in one week) at 6 months, but 76.9% of these children were successfully retrained following reimplementation of alarm procedures. Long-term follow-up found 44% of the children dry with the others wetting infrequently (the mean number of dry nights over a 10-day period was 9.92).54 A combination of the enuresis alarm with “arousal training” (if the child awakens, turns off the alarm, goes to the bathroom and urinates, and resets the alarm, then he or she is provided with a reward) was found to increase the effectiveness of alarm procedures.55 Combining alarms with imipramine or DDAVP has also been advocated for cases of refractory PNE.24,56

Most recently, the effectiveness of alarm-based treatment, desmopressin, and imipramine were compared with a no-treatment control condition.59 Two hundred and sixty-one subjects, ranging in age from 5 to 17 years old, selected from among four treatment modalities (i.e., imipramine, desmopressin, enuresis alarm, observation). The observation condition involved refraining from all fluids 2 hours before bedtime and encouraging participants to void at bedtime, conditions also in place for the other treatment conditions. Imipramine was titrated to a maximum
Primary Nocturnal Enuresis

dose of 1.5 mg/kg given 30 to 45 minutes before bedtime; desmopressin was provided 20 µg intranasally 30 to 45 minutes before bedtime to a maximum of 40 µg. Six-month treatment data and 6-month follow-up data were available for all subjects, permitting a limited comparison of the effectiveness of these interventions. Each treatment modality was superior to observation after 6 months of therapy. Follow-up data were obtained 6 months posttherapy, at which point the enuresis alarm showed statistically superior gains in dry nights compared with the other groups. The imipramine and DDAVP groups experienced considerable relapse and were no more effective at that point than the observation group.39

Summary and Clinical Recommendations

PNE will spontaneously remit in the vast majority of children, but there is no way to predict who will remit in any given year. Fortunately, effective treatment is available for most children. Children respond more rapidly to DDAVP and imipramine than to the alarm but tend to experience more dry nights posttreatment when treated with the alarm as compared with medication.24,34,39,40,57 Alarms have the most empirical evidence in support of their long-term efficacy but they typically take several weeks to work and require a high degree of child and parental compliance. As recently as a decade ago, only 3% of physicians prescribed the enuresis alarm for PNE.58

Medication is fast acting and can be fully evaluated across different titrations in a matter of days but is associated with high rates of relapse. Nevertheless, ease of administration and relative convenience may make medication the preferred intervention for families who have difficulty following behavioral protocols. Even families who tolerate PNE well or who prefer to avoid medication might consider it for occasional use (e.g., camping or sleepovers). Desmopressin is considerably safer than imipramine, with few common side effects. Significant problems such as hyponatremia are rare and easily avoided. Perhaps the major disadvantage of DDAVP is the expense, currently costing more than $100 per month, compared with imipramine at less than $10 per month, or a one-time purchase of an enuresis alarm, available for approximately $50.

Investigations of patient characteristics as predictors of successful treatment have yielded varied and contradictory results. An analysis of these findings is beyond the scope of the present paper, but trends in the literature suggest that better outcomes are associated with older children who have fewer wet nights and no daytime wetting.24,38,41,57 Additional factors have been found to influence the outcome of alarm-based interventions. Parental support and negative patient perceptions of bed wetting favor positive outcomes.59 In one study the best predictors of successful alarm treatment were: (1) children being concerned about bed wetting; (2) low levels of family stress, and (3) benign psychiatric status.60 Children who report advantages to remaining wet and who have a negative self-image are more likely to experience treatment failure.61 Parental intolerance of PNE has long been associated with poor outcomes with alarm-based treatment.61,62

Several procedures may enhance the effectiveness of treatment across modalities. Rewards for complying with procedures and for self-monitoring wet and dry nights should be included in the PNE protocol of any young child. Incentives for compliance may be more desirable than providing a reward for dry nights because early successes (i.e., dry nights) may be too infrequent for a child to receive positive feedback, thus penalizing children for a problem typically not within their control. In addition, children should participate in cleanup as much as possible. These tasks should be presented nonchalantly and not as a punitive consequence of wetting.

In considering long-term efficacy, overall cost, and safety, for compliant families who can follow behavioral protocols, the treatment of choice appears to be the enuresis alarm, followed by DDAVP, and finally imipramine. While none of these approaches works for all children with PNE, help is available, and given the psychosocial risks that may result from bed wetting, children with primary nocturnal enuresis should be considered candidates for treatment.

REFERENCES


JANUARY 1998

Downloaded from http://ojp.sagepub.com at UNIV OF NEBRASKA MED CTR on April 30, 2009

CLINICAL PEDIATRICS


18. Friman P, McGinnis JC, Handwerk ML, et al. Do children with pediatric nocturnal enuresis have clinically significant behavior problems? (Submitted for publication.)


