Nocturnal enuresis (NE), the involuntary passing of urine during sleep after the age at which bladder control would normally be anticipated, is a widespread and potentially disabling disorder for children. The treatment of NE constitutes several approaches and its pathophysiology remains unsolved. Careful consideration should be given to the work-up of NE since there may be concurrent symptoms that require attention either before or in conjunction with the treatment. Patient/family education and a cooperative approach usually produce the most favorable results in treating NE.

Enuresis is described as involuntary urination (Taber's Cyclopedic Medical Dictionary, 1977). Nocturnal enuresis (NE), also referred to as "bedwetting" or "sleepwetting," is described as the involuntary passing of urine during sleep after the age at which bladder control would normally be anticipated. This problem occupies considerable time in the general pediatric or family practice and is often accompanied by major psychosocial issues. Nocturnal enuresis is just one of the various forms of enuresis (see Tables 1 & 2). These different forms of enuresis and related topics will be discussed and referred to later in this article. The principal focus of this article, however, will be on primary nocturnal enuresis (PNE).

Enuresis is by far the most common voiding abnormality in children. Incontinence, in general, is described as being a "Cinderella" subject (Millard & Moore, 1996). Even though nobody dies from incontinence, it is hardly a glamorous condition (Millard & Moore, 1996). Most general practitioners receive little or no training about the issue, patients and families often do not want to talk about it, history taking can be time consuming, examination may be embarrassing, and the temptation to refer a specialist may be overwhelming. However, when a child can gain success with the help of the various methods of treatment, it promises to be a dream come true for him/her and the family, and the practitioner gains satisfaction as well. Despite a plethora of information found in health care journals, updates on the World Wide Web, advertisements through various media sources, and information distributed through physicians' offices, schools, and other related programs, the causes of nocturnal enuresis are still not entirely understood and management continues to be subject of controversy.

History

Nocturnal enuresis has plagued humans for centuries. It has been recognized as a problem since the time of
Papyrus Ebers, dated 1550 B.C. This was one of only a few medical texts of the time and the mere mention of NE gave some merit to its problematic nature. In a classic and frequently quoted article by Glicklich (1951), she outlines the treatment of enuresis over time and describes the cruel and barbaric methods used and the ultimate futility of the treatments. Some of these early treatment modalities include using various potions from animals, organs, or plants. For example, some remedies included placing a comb from a hen in tepid water and giving it to the child to drink or putting testicles from a hare into a glass of wine and having the child drink it. Others tried drying the comb of a cock and scattering it over the enuretic's bed. In the mid-1800s, another treatment was to induce blisters on the child’s sacrum (Glicklich, 1951). In 1927, Friedell described using psychic treatment by restricting fluids and injecting sterile water along with positive reassurance that this treatment will work. His findings demonstrated an 87% success rate and those children who did not respond were found to have low urine specific gravity at night (Friedell, 1927). This monitoring of urine concentration holds significant merit in regards to common treatment modalities used today. Punishment and public humiliation were also historically very common. Unfortunately, parents still punish their children for wetting the bed. Haque et al. (1981), found that 61% of American parents perceived bed-wetting as a significant problem and that one-third dealt with it by punishment.

Background

Because development of urinary control is a maturational process, one should understand that nocturnal enuresis is a bothersome alteration in normal development. It is important to comprehend the usual development of continence in a child. During the first stages of development of bladder control, the infant voids through a reflex mechanism. Between the ages of 1 and 2 years, there is a gradual enlargement of the bladder capacity and neural maturation of the frontal and parietal lobes occurs (McLorie & Husmann, 1987). This is the time that conscious sensation of bladder fullness develops. During the 2nd and 3rd years of life, the child is able to void or inhibit voiding voluntarily. By the ages of 4 and 5 years, maturation of the bladder should be complete, allowing the child to have an adult pattern of urinary control. The characteristic sequence for developing bladder and bowel control is as follows: (a) nocturnal bowel control, (b) daytime bowel control, (c) daytime control of voiding, and (d) nocturnal control of voiding (Rushton, 1995).

Epidemiology

At age 5, approximately 20% of children have a bedwetting episode at least monthly. The incidence decreases to approximately 10% by age 6 years with 15% of these children subsequently attaining nighttime control each year so that by age 15, only 1% to 2% of adolescents remain enuretic. The male to female ratio for NE is three to two (see Figure 1). Overall, 60% of bed-wetters and more than 90% of nightly bed-wetters are male (Schmitt, 1997).

Etiology

While there are numerous theories outlining the specific cause(s) of NE, many etiologic factors are generally recognized and accepted. Conversely, many of these continue to be cause for debate among practitioners. For many children with NE, there may not be an exclusive explanation and the findings may be multifactorial.

Genetic Factors

It is well known that there is a greater incidence of PNE in children whose parents were enuretic compared to those families with no parental history. If both parents were bed-wetters, their children have a 77% chance of having NE; and if only one parent had been enuretic, the incidence drops to 43% (Bakwin, 1993; Jarvelin, Vikevainen-Tervonen, Moilanen, & Huttenen, 1988). Recent research describes a molecular genetic heterogeneity to primary nocturnal enuresis. This genetic link is consistent with the chromosomes 13q and 12q (Arnell et al., 1997; Eiberg, 1995). Identification and gene characterization for PNE could lead to a better understanding of the complexity of urination and NE and subsequent management and treatment (Eiberg, Berendt, & Mohr, 1995).

Reduced Bladder Capacity

Bed-wetting occurs when functional bladder capacity is reached (Norgaard, Rittig, & Sjurhuus, 1989).
Children who wet the bed are often believed to have a reduced bladder capacity. This premise is based on the idea that the bladder is too small to hold all the urine that is produced at night. Urodynamic studies indicate that children with NE exhibit frequent uninhibited bladder contractions and a lower functional bladder capacity than their nonenuretic counterparts (Johnstone, 1972; Persson-Junemann, Seemann, Kohrmann, Junemann, & Alken, 1993; Pompeius, 1971; Robert et al., 1993; Troup & Hodgson, 1971). Conversely, another study revealed that bladder instability was found in only 15% of patients with isolated NE, when compared to 97% having both diurnal and nocturnal enuresis (Whitside & Arnold, 1975). Rushton (1995) noted that upon reviewing many of the studies citing abnormal urodynamic findings in children with NE (Firlit, Smey, & King, 1978; Giles, Light, & Van Blerk, 1978; McGuire & Savashino, 1984; Muellner, 1960; Starfield & Mellitis, 1968; Webster, Koefoot, Sihelnik, 1984; Zaleski, Gerrard, & Shokeir, 1973), it appears that many have included patients with noticeable daytime voiding abnormalities (including urgency, frequency, and diurnal enuresis) or with other neurologic or urologic abnormalities including urinary tract infection. Norgaard and colleagues published findings that sleep cystometries failed to equate NE with unstable bladder contractions or a reduction in bladder capacity (Norgaard et al., 1989a; 1989b). Although the topic of decreased bladder capacity in children with PNE continues to be controversial, it does appear that those children with monosymptomatic PNE rarely exhibit abnormal urodynamic findings and usually have a normal bladder capacity. This group may either produce large volumes of urine at night, thereby reaching functional bladder capacity despite normal bladder function, or may be unresponsive during sleep, or both (Jarvelin et al., 1988; Kass, Diokno, & Montealegus, 1979).

Sleep Disorders

Many parents will describe their child with PNE as being a "deep sleeper" and are confident that the inability to awaken to a full bladder is the cause of the bed-wetting. They characterize their child as difficult to awaken and unable to hear an alarm clock or any loud noises during their sleep. Wille (1994) discussed an alteration in arousal from sleep in response to the sensation of a full bladder. Broughton, in 1968, proposed the same theory. He explained further that enuretics sleep normally but suffer from an arousal disorder. Forty years ago, it was thought that bed-wetting occurred during the deep sleep stages or when transitioning from one sleep stage to another (Kales, Kales, Jacobson, Humphrey, & Soldatos, 1977; Mikkelsen & Rapoport, 1980). This presumption was studied based on the theory that the enuretic demonstrates a lack of inhibitory cerebral control of reflex voiding during deep sleep. Mikkelsen and Rapoport (1980) explained that enuresis was independent of sleep stages and occurred randomly throughout the night proportional to the time spent in each sleep stage. Norgaard et al. (1989b) studied a group using cystometric testing during sleep. They found that nocturnal enuresis occurred when the bladder was filled to capacity and it emptied with a fully coordinated voiding pattern. If the child awoke or was aroused due to a full bladder, there was an increase in pelvic floor activity (as measured by EMG using surface electrodes). However, when enuresis occurred with the sleeping child, the pelvic floor was almost electrically silent. Based on this information, they imply that enuresis treatment should be directed towards limiting urine output at night rather than sleep modulation. Parents often describe that despite their attempts to awaken the children during the night to have them void (sometimes 2-3 times), they will still be wet in the morning. Others have noted that by awakening the child shortly after he/she goes to sleep and/or early in the morning (5-6 a.m.) to void, there is a varied level of success. Most often, the child will have no recollection of ever making a trip to the bathroom. The state of confusion that the child experiences upon the forced awakening is also reported by many parents. These sometimes futile attempts inevitably make the parents very frustrated, not to mention sleep deprived. The fact that the child is a deep sleeper or difficult to arouse may be merely a characteristic and not a cause of NE given that repeated studies have shown that enuresis can occur at any stage of sleep. This element of sleep disorders may make a difference in the child's response to treatment as well as the clinician's management approach.

Sleep Apnea

Obstructive sleep apnea syndrome (OSAS) is a prevalent and potentially serious problem. Occasionally, nocturnal enuresis is an associated issue. Several case studies have reported the cessation of NE with the surgical removal of the obstructing lesion (adenotonsillectomy) or treatment with continuous positive airway pressure (Brown, Jacobs, & Pelayo, 1995; Everaert, Pevernage, & Oosterlinck, 1995; Wengraf, 1997) in both children and adults. Children who experience NE associated with sleep apnea historically snore heavily due to enlarged tonsils and adenoids. Explanations for enuresis in these situations are related to alteration in hormonal activity and renal pathology. Follenius et al. (1991) reported that urine volume and sodium

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excretion are increased at night in patients with OSAS. Baruzzi et al. (1991) found that sleep apnea caused nocturnal polyuria and an increase in the atrial natriuretic peptide secretion in the blood. In the adult population, secondary enuresis is an uncommon finding. This clinical presentation, in the event of an otherwise normal urologic evaluation, should be a clue to consider OSAS in the differential diagnosis.

Endocrine Factors

Urine output occupies a circadian rhythm in normal individuals, with a decrease of urine production normally occurring at night. Nonenuretic persons show an increase in nighttime plasma levels of the antidiuretic hormone arginine vasopressin (AVP) (Norgaard & Djurhuus, 1993). This hormone is normally excreted from the pituitary gland and its function is to enhance water reabsorption, thereby allowing the body to produce a smaller volume of more concentrated urine at night. As previously mentioned, Friedell's 1927 study monitored urine concentration in children with NE. In 1952, Poulton (1952) reported that nocturnal polyuria could be a pathogenic factor in NE. Years later, several studies expounded on this theory and reported the finding of a lower nocturnal secretion of serum antidiuretic hormone (ADH) levels in children with NE compared to normal controls. Concurrently, these children had lower mean nocturnal urine osmolalities and higher mean urinary excretion rates (Norgaard, 1989; Norgaard, Pederson, & Djurhuus, 1985; Puri, 1980). This etiologic theory remains controversial. In fact, a study by Wille (1994) could not find a clinical alteration in both nocturnal ADH secretion or nighttime urine output. Furthermore, nocturnal polyuria may be a factor in the presence or absence of abnormal ADH secretion. This endocrine-based theory may apply to some enuretics but does not account for all cases.

Psychological Factors

The question of whether psychologic disturbances are a causative factor for nocturnal enuresis is yet another controversial topic in this section. Werry and Cohrsen (1965) cited that among children with PNE, the incidence of psychopathology is relatively infrequent and there is no convincing evidence that most of these children suffer from psychoneurosis. Most enuretic children are well-adjusted and belong to a loving family (Alon, 1995). Enuresis, in its own entity, can result in psychologic, individual, and interpersonal distress (Ilyas & Jerkins, 1996). Schmitt (1997) says the idea that bad children wet their bed deliberately is a myth. Often children with PNE are labeled, teased, and sometimes punished. The shame and embarrassment they feel may be exhibited in behaviors that may cause some to think there is a factor of a psychologic disturbance. Despite their attempts (successful or otherwise) to hide the fact that they wet the bed, children are usually emotionally affected by the problem to some degree at some stage in their development. The onset of secondary enuresis may be brought about by an emotional or psychological disturbance, for example, divorce, death in the family, illness, emotional or physical trauma, or the birth of a new sibling. Even though there may be instances wherein a psychologic event may cause secondary enuresis, it is usually a matter of a relapse of physiologic enuresis (Schmitt, 1997).

ADHD

Attention-deficit hyperactivity disorder (ADHD) is a common problem of childhood. An estimated 3% to 5% of North American children are affected by this diagnosis (Bloom et al., 1993; Szatmari, Offord, & Boyle, 1989). In relation to nocturnal enuresis, it is noted that after the age of 10 years, an increase in the percentage of children with PNE will have symptoms associated with ADHD (Fergusson & Horwood, 1994). Depending on how one interprets the information in respect to a cause and effect explanation may be the source of controversy of this topic. For example, Ornitz, Hanna, and deTraversay (1992) found that among patients with ADHD, 30.2% of the 43 boys studied had persistent PNE after 6 years of age. In contrast, other reports noted ADHD in only 4% to 8% of patients diagnosed with enuresis (Mikkelsen et al., 1982; Steinhausen & Gobel, 1989). Tietjen and Husmann (1996) theorize that it is difficult if not impossible to determine whether the disruptive behavior of children with ADHD stems from the embarrassment of enuresis or whether enuresis is one of the several "soft" signs of an underlying neurologic disorder.

Diet

A very small percentage (approximately 10%) of children are believed to have a food-related allergy as a key factor in their nocturnal enuresis. Patients who were on food-restrictive diets for managing childhood
migraines and/or hyperactive behavior had cessation in their nocturnal enuresis (Egger, Carter, Soothill, & Wilson, 1992; Esperanca & Gerrard, 1969). We have found in our practice and Esperanca and Gerrard (1969) have noted that some children benefit from eliminating foods such as: those high in caffeine and sugar, citrus fruits and juices, dairy products (especially after noon), artificially colored foods and drinks, and chocolate.

Evaluation

The majority of children with NE are not at risk for future urologic problems and, therefore, it should not be considered a pathologic process (Bartholomew, 1985). However, upon a child's presentation to the health care professional with the complaint (from child and/or parent) of bed-wetting, it is of utmost importance that the initial evaluation be comprehensive to ascertain that bed-wetting is the exclusive problem. The practitioner's obligation is to rule out an organic condition. The evaluation should consist of a careful history including specific and persistent questions regarding the severity of enuresis and the circumstances in which it occurs, associated daytime voiding problems, previous urinary tract infections, constipation and/or encopresis, and pertinent family and psychosocial history. A physical examination is mandatory and must include abdominal and genital examination as well as examining the child's back to assess for obvious signs suggesting a spinal abnormality (for example, a sacral dimple, a tuft of hair, or other cutaneous anomalies). In conjunction with the spine examination, further neurologic investigation should include checking reflexes, assessing anal sphincter tone and perineal sensation, and evaluating the child's gait. If the child has a history of an altered urinary stream, observing the child voiding is important. In addition, a urine analysis and culture should be obtained (Rushton, 1989).

Based on the information gathered at the initial evaluation, it is necessary to determine the type of enuresis in order to manage it correctly. It is important to understand, categorically, the definition of terms (see Table 1) and the terminology regarding NE (see Table 2). During the initial workup, it is recommended that any findings other than uncomplicated, monosymptomatic, primary nocturnal enuresis require further evaluation (see Figure 2). The American Academy of Pediatrics recommends that radiographic evaluation be performed on patients with monosymptomatic NE if the child has a history of bacteriuria or if it is found in the workup (American Academy of Pediatrics, 1980). This is necessary to rule out other urologic abnormalities (for example, vesicoureteral reflux, hydrourephrosis, bladder instability, detrusor sphincter dyssynergia, or urethral abnormalities). Other differential diagnoses include diabetes mellitus, diabetes insipidus, renal tubular acidosis, sickle cell disease, or chronic renal failure (Moffatt, 1997). Chronic polyuria (excessive urine production) can be associated with these disease processes. Polyuria is a significant factor for some children with PNE. Schmitt (1997) describes habit polydipsia as a common cause of polyuria. These children often consume a liberal amount of fluid at dinner, bedtime, and during the night. This element plays an important role in choosing a treatment plan and the effectiveness of the prescribed approach.

Diurnal incontinence may range from a small spot of urine in the underwear, a constant leakage of urine, or a complete loss of bladder control (Fernandes, Vernier, & Gonzalez, 1991; Sher & Reinberg, 1996). Approximately 15% to 20% of bed-wetters also have diurnal enuresis, but the prevalence rapidly decreases in children over 5 years of age (DeJong, 1973). Diurnal incontinence may or may not be associated with other symptoms indicative of urgency and/or frequency that is often manifested by the child squatting, sitting on one's heel, crossing the legs, "dancing," or holding the perineum. These postures indicate a range from mild bladder instability to significant detrusor-sphincter dyssynergia. In this case, the bladder is exposed to elevated pressures when the uninhibited contraction is exerted on the voluntarily closed sphincter (Bartholomew, 1985). Hallgren's study (1957) showed that as many as 18% of children with NE and 39% of children with both nocturnal and diurnal enuresis had symptoms suggestive of bladder instability, such as frequency and urgency. This, again, demonstrates the importance of getting a valid voiding history. These daytime symptoms are classically treated with anticholinergics. There is often complete resolution in these symptoms and, occasionally, there is subsequent improvement in the nocturnal enuresis. Moffatt (1997) reports that while anticholinergic drugs may have a role in diurnal enuresis, their role in NE with daytime symptoms is not yet established. Moreover, anticholinergics usually are not the first treatment of choice by most practitioners for primary NE, as will be discussed later.

Constipation and/or encopresis (fecal incontinence) is a significant factor relating to nocturnal enuresis and incontinence in general. One study shows that between 10% and 25% of enuretics also suffer from encopresis. While nocturnal enuresis happens at night, encopresis most often occurs during the day.
Bellman, 1966; Hallgren, 1957; Katz, 1972). When the rectum is distended from constipation, it presses on the bladder wall and produces outflow obstruction that may lead to bladder instability (Brading & Turner, 1994; Fernandes et al., 1991; O'Regan, Yazbeck, Hamberger, & Schick, 1986). Loening-Baucke (1997) found that 34% of children with constipation and/or encopresis had nighttime wetting. Following the treatment and resolution of the constipation, the percentage of those still wetting the bed decreased to 12%. Needless to say, constipation issues should be addressed in conjunction with managing NE.

Treatment Modalities

Much of the rationale treating PNE revolves around improving and preserving the child's self-esteem (Ilyas & Jerkins, 1996). PNE treatment is usually initiated at or after the age of 5 years. Parents must be reassured that from age 3 years of age and up, bed-wetting is usually a maturational delay. In addition, because of the incidence of spontaneous resolution and the fact that a child less than age 5 years will usually be unaffected emotionally by NE, it is best to delay the workup and treatment. Occasionally, the bed-wetting becomes problematic for the family before the child is affected. Therefore, any treatment option should be tailored to individual family situations, parental attitudes, and beliefs. With the development of the various therapeutic modalities, it is possible that a combination of therapies may be ideal for the patient.

Education is a very important part of the initial treatment plan and should include both the patient and the family. Explanation and demystification are two very important adjuncts to education. Children and their families are often confused about bed-wetting and have a limited understanding of the anatomy and physiology of urine production, bladder function, and the nervous system (Moffatt, 1997). Many parents are surprised to learn the statistics and are relieved to know that their child is not the only 5 or 6 year old (or older) still wetting the bed. Children are often relieved, as well, to understand that bed-wetting is not their "fault" and that many children their age have the same problem. They also are glad to know that their methods of dealing with bed-wetting, until seeking medical help, are quite universal. For example, many children hide wet underwear and/or sheets in their rooms out of embarrassment or fear of ramifications (punishment, teasing by siblings, or the feeling of personal failure).

Elaborate strategic planning is often reported by children and parents in response to their methods of preparing to handle their wet bed by themselves and/or hiding the fact that they wet the bed. Some lay out items such as clean sheets, a dry towel, and clean pajamas so that the child can take care of the wetting episode either at night or upon awakening the next morning. Those who go on overnights with friends have described the careful placement of a pull-on type diaper tucked at the bottom of the sleeping bag along with a plastic bag in which to place it the next morning. Parents will often discuss the situation in confidence with the parents hosting the sleepover and, in most cases, everything works out well. Involving the child in the daily management and maintaining a "matter-of-fact" attitude assist in empowering the child while preserving self-esteem. However, even the most positive attitudes can turn to occasional frustration over time. This is usually when the family seeks medical attention.

Parents may have individual assumptions on the cause of the bed-wetting and may disagree on the appropriate approach to treatment. At times, the parents label their children as lazy and feel that the bed-wetting is intentional. Occasionally, these parental thoughts and actions come from their personal experience with bed-wetting as a child and the ensuing circumstances. A common fallacy is that when children do have dry nights, they should be able to control their wetting all the time (Moffatt, 1997). Parents should be reassured that there is no evidence that children wet deliberately or that they have deep-seated psychologic problems (Moffatt, 1989). Occasionally, some children do not know that one (or both) of their parents were bed-wetters until the time of the interview. We have found that most children are relieved and surprised by this revelation and the parents who keep this information from their child do so because of embarrassment from their previous personal struggles with NE. Conversely, family history often helps parents empathize with their child’s struggles. In our practice, children whose parents have shared their history of bed-wetting often present to clinic with a more positive approach to the problem.

Behavioral Modification

Motivational therapy is a form of behavior modification promoting positive reinforcement using praise and reward. The child is encouraged to assume responsibility and take an active role in the treatment program. A
behavioral chart ("star chart") is used to keep track of dry nights and the parents and clinician provide positive reinforcement and/or rewards (for example, a toy, money, a special outing). The cure rate for motivational therapy alone is estimated at 25% (Schmitt, 1997); however, "marked improvement" in greater than 70% of patients has been reported (Marshall, Marshall, & Lyons, 1973). Monda and Husmann (1995) reported that 18% of their study group became completely continent during a 1-year treatment period using the star chart and motivational therapy alone. This is similar to the spontaneous resolution rate for PNE without treatment. The principles of motivational therapy can be incorporated into other therapeutic regimes such as conditioning and pharmacologic therapy.

Conditioning therapy uses an enuretic alarm system. This regimen is the most commonly recommended form of therapy as described in the medical literature. It has a success rate of 65% to 75% and relatively low rates of relapse (Alon, 1995). The enuresis alarm is a system using a signal alarm that is triggered by contact of urine. Its premise is to teach the child to awaken to the sensation of a full bladder. The bell-and-pad alarm system is an older system wherein the child sleeps on a sensory pad. The alarm is set off only after the child has soaked through the undergarments. The newer systems are attached to the clothing at the site of the perineum and is triggered at the beginning of urination rather than after the child has partially or completely emptied the bladder. The conditioning aspect of awakening along with the repression of voiding is gradually elicited by repetitive association of awakening to the alarm. Several alarms are available that are portable and easy for the child to operate independently. Most of these systems have an audio alarm that emits 80 db sound. A tactile alarm is available that vibrates upon sensation of wetness (much like a silent business pager). This is worn near the bladder and has the advantage of alerting the child and not awakening the rest of the household, as is often the case with the audio alarms.

Benefits of this system are the high success rate (if used persistently) and the low relapse rate. Those children that do relapse often respond to a short second course of treatment with the alarm. Many parents like the idea of avoiding medication and consider this a major advantage when choosing the alarm over other forms of therapy. It should be stressed to the parent that using the alarm requires persistence and patience and that it is not a "quick fix" to the problem.

Disadvantages of alarm system are that they are time intensive and require a high level of motivation and cooperation from the child and the family for at least 3 weeks and as long as 4 to 6 months (Dische, 1971; Forsythe & Redmond, 1970; Schmitt, 1982; Wagner et al., 1982). Relapses may occur if the alarm is discontinued too prematurely. It is recommended that the child continue to wear the alarm until he/she is dry at night for 4 weeks rather than a shorter dry period (Forsythe & Redmond, 1970). A recurrent frustration for the family is when the child does not awaken to the alarm. The child must be reminded of the program goals of self-awakening. If the child is a deep sleeper and the family wishes to continue with the program, it is the parent's responsibility to enter the child's room as quickly as possible in response to the alarm, awaken the child, and encourage him/her to get out of bed and proceed to the bathroom to finish urinating. If the alarm system fails, it is most often that the treatment was not given the appropriate amount of time, motivational therapy was not concurrently applied, or that the child did not want to continue with the program. Studies from the 1970s and 1980s report that fewer than 5% of physicians used behavioral treatment in favor of pharmacotherapy (Blackwell & Currah, 1973; Carter & Brookfield, 1996; Foxman et al., 1986; Rushton, 1989; Shelov et al., 1981). This is most likely related to the time-consuming instructions that must be given to the family as well as the close followup and cooperation required among the physician, patient, and family members (Miller, Goldberg, & Atkin, 1989). However, Schmitt (1997) cited that over the past 10 years, the recommendation of alarms by pediatricians has increased from 5% to 80%.

Bladder-Retention Training

Bladder-retention training is based on the presumption that the child has a decreased functional bladder capacity. To establish a baseline, it is helpful to estimate normal bladder capacity for each age group using the formula: Bladder capacity (in ounces) = Age (in years) + 2 (Berger et al., 1983; Blackwell & Currah, 1973; Koff, 1983). Retention training involves conscious attempts at "bladder stretching" by voluntarily prolonging the intervals between voidings (Rushton, 1989). This technique also involves keeping a daily log of voided volumes, forcing fluids during the day, and stream interruption. The basis for this treatment is the postulation that an increase in the bladder capacity will improve or eliminate the enuresis. The element of fluid restriction in the evening is often discussed by parents. Many parents, out of desperation, limit fluids well before bedtime. At times, this may work but most find that it is a source of frustration and that it often produces a conflict between the parent and child. Statistical evidence has shown that fluid restriction is not

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effective (Hagglund, 1965). The cure rate for bladder retention training is only 35% (Starfield & Mellitis, 1968). This is probably due to the demanding nature of the program and the element of bladder instability and urinary frequency/urgency seen in some of these children.

**Pharmacologic Therapy**

A number of medications have been used to treat nocturnal enuresis. Imipramine (Tofranil) and desmopressin acetate (DDAVP) have proven successful. Some credence has also been given to oxybutynin (Ditropan). Pharmacologic treatment for NE is best viewed as management therapy rather than a cure. This is because of the high relapse rates reported after short-term treatment with pharmacotherapeutic agents. Therefore, most patients require long-term therapy either continuously or on an as-needed basis (Rushton, 1995). Children who use these medications on a PRN basis have an immediate response with a single dose. Therefore, some choose to reserve the use of this regime for special occasions such as sleepovers or camp. Imipramine is a tricyclic antidepressant that is theorized to affect NE through three modes of action: (a) alteration in arousal and sleep mechanisms, (b) anticholinergic and antispasmodic effects, and (c) antidepressant action (Banerjee, Srivastav, & Palan, 1993). Imipramine may also work by increasing ADH secretion from the posterior pituitary (Puri, 1986). It is taken 1 to 2 hours before bedtime and the duration of action is 8 to 12 hours. Starting doses are usually 25 mg per day with a maximum dose of 50 mg per day for children 8 to 12 years of age. Children greater than 12 years of age can generally tolerate 75 mg per day if needed (Schmitt, 1997). After initiating therapy, 10 days to 2 weeks should pass before evaluating the response or adjusting the dose. Imipramine is often prescribed for 3 to 6 months with a gradual wean thereafter. However, many patients require the medication for many months if a trial cessation of therapy prompts a relapse. Initial success rates are as high as 50%. Some studies, however, note a combined long-term cure rate of only 25% once the medication is stopped (Blackwell & Currah, 1973).

Side effects are somewhat uncommon and include dry mouth, nervousness, insomnia, mild gastrointestinal disturbances, and personality changes (Alderton, 1970; Kardash, Hillman, & Werry, 1968; Shaffer, Costello, & Hill, 1968). A great concern with imipramine is the possibility of an overdose. This medication should only be dispensed by an adult and the medication should be kept out of the reach of toddlers. Overdoses can cause myocardial effects (arrhythmias and conduction blocks) and hypotension (Fouron & Chicoine, 1971). Deaths and drug overdoses from imipramine have been reported in the younger siblings of patients (Goel & Shanks, 1974; Parkin & Fraser, 1972; Penny, 1968). Despite the significant response from imipramine, it should be used with caution and the family counseled on the need for prolonged therapy and the precautions surrounding its administration.

Desmopressin acetate (DDAVP) is a synthetic analog of vasopressin and acts by reducing the urine production thereby increasing water retention and urine concentration in the distal tubules (Schmitt, 1997). Through the mechanism of concentration of urine and a decrease in the nocturnal urine volume, it is believed that the child will not reach his/her bladder capacity. This theory assumes that when the child wets at night, he/she exceeds the bladder volume (Norgaard, 1989). Desmopressin has been used intravenously in treating central diabetes insipidus, hemophilia A, and von Willebrand's disease. For many years the intranasal form has been used as an antidiuretic treatment for central diabetes insipidus (Bellman, 1966; Ward & Fraser, 1974) and was introduced for treating NE in the 1970s in Europe (Matthiesen, Rittig, Djurhuus, & Norgaard, 1994). DDAVP received approval from the Food and Drug Administration (FDA) in 1990 and has since gained widespread use in the United States (Rushton, 1995). This medication is particularly effective in those patients with NE who do not manifest normal diurnal rhythm of ADH secretion with a resultant decrease in nocturnal secretion and therefore a higher urine output at night. The effect usually lasts 6 to 12 hours, but may continue up to 24 hours, especially in young children and geriatric patients (Beach, Beach, & Smith, 1992; Richardson & Robinson, 1985). DDAVP is available in a nasal spray pump which delivers 10 mcg per spray (Harris, Hedner, & Vilhardt, 1987). The initial recommended dose for treating NE is 20 mcg (one spray in each nostril). Some children respond to as little as 10 mcg while others require up to 40 mcg (two sprays in each nostril) for maximum effectiveness.

As of March 1998 the FDA approved the tablet formulation of DDAVP for managing PNE in children ages 6 and over (Rhone-Poulenc Rorer, 1998). Oral desmopressin comes in 100 and 200 mcg (0.1 to 0.2 mg) tablets and the recommended dose ranges from 200 to 600 mcg (0.2 to 0.6 mg) to achieve the desired response. Several studies reported favorable results with the oral form of DDAVP. These studies demonstrated comparable results when compared to intranasal DDAVP (Janknegt et al., 1997; Matthiesen et al., 1994; Skoog, Stokes, & Turner, 1997; Stenberg & Lackgren, 1994). Patients may prefer this form if they
experience nasal congestion from the nasal spray which would, in turn, impede medication absorption. Additionally, some children may find it difficult to independently administer the nasal spray. Another factor is that the tablet form is much more discreet than the nasal spray, and usually doesn't require an explanation if the child is taking the medication in the presence of others.

Immediate results are often seen with this medication. The literature, however, cites that the reported range of response to DDAVP varies from 10% to 91% (Moffatt et al., 1993). Husmann (1996) determined that if DDAVP was used for monosymptomatic NE, 68% had a full response. If used with patients with both diurnal and nocturnal enuresis, only 19% were dry. The response to DDAVP also appears to be dose related (Klauber, 1989; Post et al., 1983).

The length of treatment varies with each patient and is clinician dependent. Some treat for 2 weeks and taper the dose while others treat for months at the effective dose with periodic trials without the medication to assess for dryness. Relapse rates after discontinuation of short-term therapy are high (Moffatt et al., 1993) and can be frustrating for the family. To reiterate that this form of therapy is not used as a long-term cure but rather as management therapy may be helpful. DDAVP treatment is often indicated for substitutional therapy (Norgaard, Jonler, Rittig, & Djurhuus, 1995). In the children who achieve immediate results with DDAVP, its use is often reserved for overnight stays away from home. Considering the 15% annual rate of spontaneous resolution, those who choose long-term use of DDAVP and find they are dry when the medication is stopped probably fall into the category of "outgrowing" the bed-wetting. Most insurance companies cover the cost of DDAVP. However, some insurance companies require prior authorization and require the child to meet certain criteria before approving its use (personal experience). This criteria most often includes the child's age (often needs to be 10 years or older) and the trial of other forms of therapy (behavior modification, fluid restriction, or previous medications). One report cites the cost of DDAVP to the insurance company ranges from $100 to $105 per month (Carter & Brookfield, 1996).

Most pharmacies charge between $80 and $100 per vial of DDAVP nasal spray and the cost of the tablets is approximately $2.80 per 200 mcg (0.2 mg) tablet (personal correspondence). Some families whose insurance company does not cover the cost opt to pay full price for the medication because they are so pleased with the results for their child. These are also the families that usually reserve its use for overnight stays away from home.

DDAVP is safe if used correctly. Some reported side effects of the nasal spray are nasal congestion, rhinitis, mild headache, and epistaxis (Carter & Bookfield, 1996). DDAVP tablets have a reported side effect of mild headache. There have been rare cases of significant hyponatremia secondary to water intoxication (Bamford & Cruickshank, 1989; Beach et al., 1992; Kallio, Rautava, Huupponen, & Korvenranta, 1993; Simmonds, Mahony, & Littlewood, 1988; Yaouyanc et al., 1992). Most of these cases were due to an excess of fluid intake in conjunction with the medication. It is of the utmost importance to assure that the patient and family understand the importance of fluid restriction in conjunction with taking the medication. By explaining the action of desmopressin (the temporary reabsorption of water from the kidney), most will comprehend the importance. Parents should also be alert to some early signs of water intoxication in order to seek early medical attention. These signs may include an altered level of consciousness, blurred vision, confusion, disorientation, and frontal headache. Usually, progression of symptoms is indicative of a drop in the serum sodium level and is often followed by a seizure (Bernstein & Williford, 1997). Prior to prescribing DDAVP, the clinician must assess the presence of other factors such as cystic fibrosis, renal disease, endocrine disorders, or other disorders that may produce electrolyte imbalances. Psychogenic polydipsia and habit polydipsia (Schmitt, 1997) should be considered due to the risk of water intoxication and hyponatremia (Bernstein & Williford, 1997; Thompson & Rey, 1995). Patients and families must also be warned that DDAVP should not be used in instances where fluid and electrolyte balance would be affected, such as fever, viral illnesses, vomiting, or diarrhea. Increased fluid intake is required for treating these situations which would deem the intake of DDAVP dangerous.

Anticholinergic medications, specifically oxybutynin (Ditropan), have the properties of a musculorelaxant (thereby reducing uninhibited bladder contractions) as well as producing local anesthetic effects on the bladder. Theoretically, this medication could help the bed-wetter by increasing the bladder capacity (Husmann, 1996). This modality may be helpful to those children with NE who also present with daytime frequency/ urgency and/or incontinence. Success rates of 90% have been reported (Kass et al., 1979) for enuretic children with significant daytime incontinence and/or bladder instability. However, anticholinergics are rarely beneficial for children with exclusive nocturnal enuresis (Lovering, Tallett, & Mckendry, 1988).
Combination Therapy

When an individual form of therapy is not effective, combination therapy is often considered. One form of combined modalities include desmopressin, behavior modification, and the enuresis alarm (Sukhai, Mol, & Harris, 1989). The motivation for this combination is patient/parent satisfaction due to the fact that desmopressin may have an immediate effect and the enuresis alarm may take up to 3 weeks to see a decrease in wet nights (Wille, 1986). Parents often stop using the enuretic alarm in the early treatment period because of continued enuresis (Monda & Husmann, 1995; Wille, 1986). By initiating desmopressin at the onset of alarm therapy, it is believed to improve compliance. One report shows that after 3 weeks of enuresis alarm/desmopressin combination a slow wean of the desmopressin and subsequent therapy of the alarm and behavior modification can effect a cure of the enuresis (Ilyas & Jerkins, 1996). Combining DDAVP and imipramine has been successful in some patients with refractory primary nocturnal enuresis (NE that has proven resistant to other forms of therapy). The positive effect is due to the synergistic action between the two medications (decrease in urine production, increase in bladder capacity, and easier awakening) (Reinberg & Vaughn, 1996).

Psychotherapy

Psychotherapy has been used as a treatment for enuresis without convincing evidence of its effectiveness. Werry (1967) reiterates that the majority of primary enuretics do not suffer from underlying psychoneurosis. Because prolonged psychoanalysis is generally an inefficient and unnecessary approach for children with PNE, it should be limited to children with obvious psychopathology (Fraser, 1972; Perlmutter, 1985).

Hypnotherapy

Hypnotherapy is not based on conditioning therapy. It involves the explanation of the bladder-brain connection and teaching self-hypnosis and visual imaging to the child in responding to a full bladder during sleep. One controlled study comparing hypnotherapy with imipramine reported a 76% dryness rate after initiating both types of therapy. After 9 months, 68% of the hypnotherapy group remained dry in comparison to only 24% in the imipramine group (Banerjee et al., 1993). If clinicians are interested in this form of treatment, they must be trained and certified by the American Society for Clinical Hypnosis (Moffatt, 1997).

Summary

Nocturnal enuresis is a widespread and potentially disabling disorder for children. The treatment of NE constitutes several approaches and its pathophysiology remains unsolved. Careful consideration should be given to the workup of NE since there may be concurrent symptoms that require attention either before or in conjunction with the treatment. Patient/family education and a cooperative approach usually produce the most favorable results in the treatment of nocturnal enuresis.

References


http://www.duj.com/Johnson.html


### Definition of Terms - Enuresis Categories

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<tr>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>Diurnal enuresis</td>
<td>Wetting that occurs during waking hours (daytime incontinence).</td>
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<tr>
<td>Nocturnal enuresis</td>
<td>Wetting that occurs during sleep.</td>
</tr>
<tr>
<td>Uncomplicated enuresis</td>
<td>Nocturnal enuresis, normal physical examination, and negative urine analysis and urine culture.</td>
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<tr>
<td>Complicated enuresis</td>
<td>Secondary onset of enuresis, history of urinary tract infection(s), abnormal neurologic examination, and a history of voiding dysfunction.</td>
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### Nocturnal Enuresis Terminology

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<th>Term</th>
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<tr>
<td>Primary</td>
<td>Bed-wetting since birth without any significant periods of dryness.</td>
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<tr>
<td>Secondary</td>
<td>Onset of bed-wetting after the child has been dry for at least 6 months.</td>
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<tr>
<td>Monosymptomatic</td>
<td>Nocturnal enuresis that occurs with normal daytime urination.</td>
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<tr>
<td>Polysymptomatic</td>
<td>Nocturnal enuresis associated with urinary frequency, urgency or other signs of bladder instability.</td>
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