

REVIEW ARTICLE

Nocturnal Enuresis: A Synopsis of Behavioral and Pharmacological Management

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ABSTRACT

Nocturnal enuresis (NE) is involuntary urination that occurs at night during sleep without any inherent suggestion of frequency of bedwetting or pathophysiology. For this review, a thorough internet search was done using the search engines of PubMed, Scopus, PsycInfo, ScienceDirect, and Google Scholar. In this review, we glow the light on new-insights of behavioral treatment of nocturnal enuresis. The management of nocturnal enuresis has converted from a strictly psychopathological perspective to a bio-behavioral perspective in the past few decades. There are a number of treatment options are available for NE; such as drug therapy, bladder training, auro therapy, positive reinforcement, and the enuresis night alarm. Enuresis night alarm therapy, is presenting lower rates of relapse in the long term, higher cure rate and therefore being considered a gold standard treatment for enuresis, but it is a conditional treatment; it requires patience, persistence and motivation. Several behavioral approaches can be used for treatment such as enuresis night alarm therapy and various skills oriented components, we must do physical examination and rule out a specific medical or organic etiology, as well as urine test should be negative.

Keywords: Nocturnal enuresis, bedwetting, enuresis night alarm therapy, pajama device, imipramine

INTRODUCTION

Nocturnal enuresis (NE) is defined as “involuntary voiding of urine that occurs while sleeping that can happen at an inappropriate and socially unacceptable time and place” (van Kerrebroeck P. et al. 2002), and due to which its negative impact occurs on the quality of life of the affected children and their families. It is most common in boys, with a ratio of three boys for every girl until the age of 15 (Thiedke CC, 2002).

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Received: 02 January 2018 Accepted: 09 February 2018

Sleep and Hypnosis

Journal homepage:

www.sleepandhypnosis.org

ISSN:1302-1192 (Print) 2458-9101 (Online)



Approximately 15 percent of children at the age of 5 have enuresis. Every year of maturity resolution occurs in 15 percent of all cases. Therefore, 8 percent of 12-year-old boys and 4 percent of 12-year-old girls are enuretic (Forsythe WI., 1989). However, only 1 to 3 percent of adolescents is still wetting their bed and still has to deal with enuresis (Rogers J, 2003). Even though its discomfort but does not bring risks to physical health. Enuresis leaves its impact on an emotional and social level, and leads to stress and inconvenient situations in the lives of the affected and their families (Fitzwater D & Macknin ML, 1992).

Enuretic episodes commonly occur in all stages of non-rapid eye movement (NREM) sleep and their occurrence depend upon the amount of time spent in each stage and rarely occur during REM sleep. One study said bedwetting as the third most stressful life event, after parental divorce and parental fighting

(Mellon, M.W., 2000). Enuresis may be comorbid with mood and emotional disorders and also has a high level of comorbidity with attention deficit hyperactivity disorder (ADHD). Part of emotional disorder such as anxiety, expression and insomnia are experienced by persons who have elimination disorders related to distress and social stigma. Initially enuretic children face problems from being provoked and teased by siblings, then being punished by parents, that affects disturbed relationship with their parents and family members (Shreeram, S., et al. 2009). Several studies have found that self-esteem ameliorate with management of the behavior (Neveus T, et al. 2006) and this could be lead social isolation and this negative impact becoming more significant from the age of seven (Arantes MC, & Silvaes EFM, 2007). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), classifies both enuresis and encopresis under the heading of elimination disorders (American Psychiatric Association DSM-5, 2013).

Classifications

Enuresis classified on the basis of the time of occurrence into the following three subtypes:

- Nocturnal Enuresis: Passing urine during sleep.
- Diurnal Enuresis: Leakage of urine during waking hours.
- Monosymptomatic or uncomplicated NE: Normal voiding at night with absence of symptoms.
- Polysymptomatic or complicated NE: Bedwetting at day time with symptoms urgency, frequency, constipation and encopresis.
- Nocturnal and diurnal Enuresis, also known as non-mono-symptomatic enuresis.

The incident rate of nocturnal enuresis decreases from 20 percent in 5-year-olds to 2 percent in adulthood (Ju, 2013). Diurnal enuresis always associated bedwetting more in girls while nocturnal enuresis associated in boys.

According to National Institute for Health and Clinical Excellence (NICE) clinical guideline (2010) nocturnal enuresis can be classified;

- Primary enuresis: If Children more than 5 years who never had bladder control is called primary NE.

- Secondary NE: If children who are potty trained and no bedwetting for 6 month and starts wetting the bed again is called secondary NE.

According to the international children's continence society (ICCS) criteria, enuresis defined an intermittent wetting during sleep in children after their fifth birthday.

Etiology

NE has multifactorial causes; from the difficulty in waking up when the bladder is filled; to excessive nocturnal urine production and nocturnal bladder hyperactivity. The main etiology for nocturnal enuresis can be drinking late in the evening or not passing urine before going to sleep, resulting in excessive urine volume. NE is hereditary, children whose parents were not enuretic have only a 15% incidence of bedwetting and when one or both parent were enuretics, the rates increases to 44% and 77% respectively (Yeung CK, 2003, Neveus T, 2008, Yeung CK, 2008). Another cause may be a low amount of antidiuretic hormone during the night which controls the production of urine. Some studies said that the majority of elimination disorders are functional, such as it is not due to neurological, structural or medical causes (von Gontard & Neveus, 2006). Psychological disorders, externalising conditions such as attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) and internalising disorders such as depression has 20%-40% of all enuretic children. These comorbid conditions needs separate assessment and treatment – in addition to the symptom-oriented treatment of the child's elimination disorder.

Goals of treatment

The following are goals of management for NE (Kidoo D, 2007 & Schmitt BD, 1997):

- To stay without bedwetting on particular occasions such as sleepover at night or day.
- To decrease the frequency of wet nights.
- To decrease the impact of enuresis on the child and family.
- To avoid recurrence of bedwetting.

For achieving the above goals lifestyle and behavioral changes play an important role.

Primary management of enuresis is behavioral modification and positive reinforcement and it should be start with educating the child as well as parents about the condition. Drug therapy such as desmopressin acetate and tricyclic antidepressant like imipramine is also effective. The combination of nocturnal and diurnal enuresis (non-mono-symptomatic enuresis) may be more difficult and time-consuming to treat (Rittig N, et al. 2013 & Vande Walle J, et al. 2012).

Behavioural Management

There are different types of behavioral therapy options available for bedwetting. Motivational therapy; it includes reassurance, emotional support, removing guilt, and encouraging the child should be without bedwetting. Simple behavioral interventions; include to wake up the child to void at times usually associated with bed-wetting. Positive reinforcement; it is for desired behavior such as sticker or star charts and children should give reward for dry night. Bladder training; it is to reduce fluid and caffeine intake before going to bed. Enuresis alarm therapy and medications may be more effective but have potential side effects. The management of voiding of urine should be started from the age of 7 year in boys and 5 year in girls (Neveus T, et al., 2010) because the difference in ages is due to the lower incidence of NE, higher motivation, and advanced maturation in enuretic girls versus boys. The night urine alarm behavioral treatment is considered the gold standard for enuresis. It is highest cure rate in the long run (Netley C, et al. 1984). Other behavioral treatment such as penile binding, buttock and sacrum burning, and forced urine-soaked pajama wearing reported in a review of ancient approaches to NE (Glicklich, 1951) but it is called aversive treatment. The evolution of treatment for NE that start in early in the 20th century but given up due to the physically harsh treatments, in favor of approaches that were more humane from a physical perspective but still problematic from a psychological one.

Night urine alarm therapy

Night urine alarm therapy is a conditioning type of treatment option for NE. The first user of this treatment

was Herbert Mower (Mower & Mower, 1938). Psychological research on medically uncomplicated NE on children was done in mid-1970. It has been based on alternative behavioral procedures such as operant conditioning or improving urine alarm treatments (Houts, 2000; Mellon & McGrath, 2000). One more study said that the cure rates for enuresis of night alarm is two thirds, and its relative risk of failure rate is 38% (Glazener Cathryn MA, et al. 2005). The night urine alarm device is based on the behavioral therapy technique and it make an effort to wake up the child when the bladder is full (Meneses R, 2001). Even though it is gold standard therapy the treatment effect and response rate of night alarm are not immediate and treatment should be continued for 2–3 months or until the child is dry for 14 consecutive nights. Controlled studies on urine alarm reported that this simple device 65 to 75 percent effective, with duration of treatment around 5 to 12 weeks, and 6-month relapse rate of 15-30 percent (Butler, 2004).

The device is associated with a moisture sensor and it is connected to a sound system which combined with other stimulus that gives an alarm if the child has urinate in bed and has been detected by the sensor (Meneses R, 2001). This theory begins to develop the awareness of a full bladder during sleep, and to stop to urinate in bed and the child would get up from the bed and go to the toilet to urinate. During this procedure parent should play important role such as encourage and motivate the children, and also important to treat the children involved with care and proper intention. Also during the recurrence of episodes of bed-wetting; parents need to show a lot of support, patience and tolerance to them. One more test for parents to convince the enuretic children and bring them to the bathroom once the alarm is activated (Meneses R, 2001), it is very difficult and tedious job faced by the parents to get a fruitful result such as the child can quit from the episode of bedwetting (Rogers J, 2003). It is not only important to improve support from the family and parents but also should to have a positive approach during dealing with a child and the treatment. Also need an improved relationship with the health service during treatment and patient compliance and self-care and support (Ciccone MM,

2010). As described earlier it is gold standard treatment option of enuresis for long term use, and such devices could be incorporated to enuresis therapy and possibly improve results. There are two types of night urine alarm such as bed devices and pajamas device. Most of this research has been conducted using the bed device and, more rarely from the pajama device.

Mechanism of action of Night urine Alarm Device

The mechanism of action in alarm treatment is based on classical conditioning, as it was initially described. In this classical conditioning alarm is as the unconditioned stimulus, bladder distention as the conditioned stimulus and waking as the conditioned response (Mowrer & Mowrer, 1938). More recent literature highlight a negative reinforcement or avoidance paradigm (Friman, 1995; Friman & Jones, 1998) in which the child increases sensory awareness to urinary need and exercises anatomical responses such as contraction of the pelvic floor muscles, that effectively avoid setting off the alarm (Mellon, Scott, Haynes, Schmidt, & Houts, 1997). Cure rate of this method gets slowly; however, and during the first few weeks of alarm use the child often awakens only after voiding completely. The aversive properties of the alarm, however, inexorably strengthen those skills necessary to avoid it.

Bed Devices

The bed device associated with two aluminum foil pads, one of which is perforated, with a cloth pad between them. The device out on the bed and the bed pads are keep under the sheets of the enuretic child's bed with the perforated pad put on top. During this mechanism urine seeping through perforations in the top pad, then collecting in the cloth pad, and causing contact with the bottom sufficient to complete an electrical circuit then it activate a sound-based alarm. The principle of this method is that, the awakened child turns off the alarm and completes a series of responsibility of training steps associated with their accidents (Friman & Jones, 1998), such as completing urination in the bathroom, changing pajamas and sheets, and returning to bed. In clinical

practice, the alarm always alerts parents first, who awaken the child and guide them through the training steps.

Pajama (Under wear) Device

Pajama devices are similar in function as bed devices but in addition it is simple in design. In this method pajama or special underwear was evolved. The mechanism is based on to get electrical stimulation after complete an electrical circuit. This device contained both the moisture sensor and the electrodes for electrical stimulation, when the child began to urinate. The alarm itself is either placed into a pocket sewn into the child's pajamas or pinned to them and two wire leads extending and the alarm are attached by small alligator clamps on or near the pajama bottoms. When the child wets during the night, absorption of urine by the pajamas completes an electrical circuit between the two wire leads and activates the alarm. The stimuli are extending a great distance from one side to the other and it is in the form of buzzing, ringing, vibrating, and lighting. The principle of this device same as the bed device, as the alarm is supposed to waken the child and completing urination in the bathroom.

There are four types of nocturnal alarms explained in studies, these are the sound (Glazener Cathryn MA, et al. 2002 & Ozgur B C, et al. 2009), the vibration (Tobias NE, et al. 2001) which combines an electrical impulse with a sound (Hojsgaard A, et al. 1979) and code words (Barroso U, et al. 2014). The most commonly used alarm is the one that produces a sound, and device that has been tested with different volumes, with or without associated light. Humidity sensor should keep on the bed or in the child's underwear (Glazener Cathryn MA, et al. 2002). The vibrating alarm also tested in studies and consisted of a small device that was set in the inner clothing tab of child, it directly contact with the skin. It is used in both boys and girls.

There is unacceptable and unsatisfactory side effects were noted in many studies; such as fear, burns and other skin lesions, due to which they discontinue the use of alarms by users and their caregivers. The monophasic electric current used in some studies, that causes higher risk of skin lesions. Recently, one of study group published

a different alarm mode associated with electrical stimulation. In such case, two self-adhesive electrodes keep in the perianal region with a humidity sensor inside the underwear. When the child start urinates, electrical stimulation triggered a contraction of the pelvic floor muscles in order to stop the urination. After the 20 seconds, the alarm sounded to try to wake up the child (Hojsgaard A, et al. 1979). A more recent alarm system was described by the University of Sydney, Australia this technique is based on the association of the buzzer with code words, recorded by parents on the device. In such case, children are rewarded when they remember the word that was recorded by the device with the voice of the parents before the night, instead of being rewarded for having a night without the episode of bedwetting. The motivation and positive approach is an important factor during the awakening process of individuals, and by using a code word at night decreases the threshold to raise these children, by activating them in a playful way, by a game (Barroso U, et al. 2014).

Other methods

Waking schedule- in this method wakes up the child prior to bedwetting and guides them to go to the bathroom for urination. In this method parent play an important role. There are many important schedules for children as well as parent, waking the child just before the parents go to bed and systematically waking them one-half hour earlier on nights following several successive dry nights, until the child awakens to urinate without assistance. Self-monitoring- the child should be monitor himself and keep a record on a calendar whether the previous night was wet or dry. Keep a tracing paper over the stain that was getting from bedwetting and trace the outline of the stain then the tracing paper put over a grid, and the number of squares inside the area is recorded, (Friman, 1986, 1995) this is a more complex and sensitive method. There are many other simple behavioral therapies such as reward systems or waking a child to void in the toilet (Glazener CM & Evans JH. 2004). Punishment and humiliation should be avoided by parent (Houts AC, et al. 1994). Dry bed training is a operant than classical conditioning model, as described by Azrin and Thienes

(Azrin NH, et al. 1978), is a more labour-intensive parent-awakening technique and may be slightly more effective in combination with alarm therapy than alarm therapy alone (Glazener CM], et al. 2004). Dry bed training combines variety of techniques these are Retention control training (RCT); enlarging bladder capacity, Cleanliness training; mild punishment and self-correction following an accidental wetting, Night-time wakening; arousal through bladder proprioception and differential positive reinforcement for dryness; feedback and motivation. Other Kegel or stream interruption exercises and paired associations, but results are not up to the point.

Pharmacological Management

Medication should be started in children around seven years and older only if non-pharmacologic measures not successful. There are two primary drugs used for treatment of NE, desmopressin and imipramine. Anticholinergic agents also use for NE.

1. Desmopressin acetate: It has been studied for use in enuresis since the 1970s. It is a synthetic analogue of antidiuretic hormone (ADH), the onset is quick and longer, with more antidiuretic action (Djurhuus JC, et al. 1998). The side effects usually are mild, such as headache, fatigue, nausea and abdominal pain, as well as stuffiness and epistaxis for the nasal preparation. Desmopressin acetate may be prescribed at doses from 200 µg to 600 µg. It is also available nasal spray at doses 0.1mg/ml (5ml): Delivers 10mcg/spray.

2. Imipramine hydrochloride: Imipramine hydrochloride is a tricyclic antidepressant, but its mode of action in the treatment of enuresis is unclear. Its anti-enuretic response is often immediate. Imipramine makes the bladder less sensitive to filling so it allows holding more urine before urinary urge (Stephenson, 1979). The recommended starting dose of imipramine is 25 mg for children 6 to 12 years of age and 50 mg for those older than 12 years. It should be given 1 to 2 hours before bedtime. Its response rate during treatment is similar to that with desmopressin acetate, and the cure rate after treatment is similarly comparable with placebo (Glazener Cathryn MA, et al. 2005). Minor side effects are common,

and children should be monitored for personality changes, including emotional lability, irritability and anxiety. Other effects include headaches, changes in appetite and disturbed sleep patterns, but serious side effects are convulsions, coma and cardiac arrhythmias from overdose but it is rare.

3. Anticholinergic agents: Indications anticholinergic medications are dysfunctional voiding, overactive bladder, and neurogenic bladder. Mechanism of action of these medications reduces uninhibited detrusor contractions, increase the threshold volume at which an uninhibited detrusor contraction occurs, and it enlarges the functional bladder capacity. The drug of choice of this setting is oxybutynin chloride and tolterodine are commonly prescribed. Oxybutynin chloride also has antispasmodic and analgesic properties and its anticholinergic adverse effects are dry mouth, blurred vision, facial flushing, constipation, poor bladder emptying, and mood changes. Constipation is a problematic side effect that might be increase the risk for wetting. Oxybutynin is another anticholinergic agent should give at dose of 2.5-5 mg and administer at bedtime. A long-acting preparation is also available but has not been approved for use in children. Tolterodine is an antimuscarinic drug not approved for use in children younger than 12 years. Flavoxate, is a smooth muscle relaxant (urinary spasmolytic), it might be helpful in some patients with overactive bladder and dysfunctional voiding but is approved only for children older than 12 years.

Above medication should be prescribe for enuretic children for 4 weeks and follow up should be done, after 4 weeks of taking the medication, if found effective the treatment should be continued for 3 months, after that it should be stopped for a week and check if the child still has NE without the medication. The medication should

be continued for another 3 months if bedwetting has not stopped. If children do not respond to one or more measures should get benefit from combined treatment strategies such as, combining non-pharmacologic and pharmacologic treatment or multiple pharmacologic therapies. Ideally the pharmacology treatment should be continued with bedwetting alarm and along with lifestyle changes.

CONCLUSION

Encouragement, a positive attitude and motivation are important components of treatment to become dry. Punishment and criticism has no role to play in care. Children with enuresis get always benefit from a caring attitude of parents. A positive approach by the physician and care taker is also important role to play for putting confidence and to increase compliance. If NE is not treated properly, it will continue for many years and, in some cases, up to young adulthood, due to which it leads disruption of family life and it put negative social consequences. Urine alarm is gold standard and an old therapy, it can easily use, highly effective method for managing enuresis. Behavioral modification with positive reinforcement get better treatment results but enuretic need regular follow-up to get therapeutic results. To conclude this article, we have found that there is no important difference between the types of alarm in terms of efficacy. One of the pilot study said that the electrical stimulation seem to have the potential to bring a faster response to adolescents with enuresis (Hojsgaard A, et al. 1979). All the therapies try to wake the child in proper time, to make continuation of urinating on the toilet, or to inhibit bladder contraction and to continue to sleep without urinating.

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