Republic of Iraq Ministry
of Higher Education and
Scientific Research University of
Diyala College of Medicine

# Nocturnal enuresis

Presented By: Sayf Talib Mahmod
Supervised By: Prof. Dr. Mehdi Shemkhi Jebr

2020_2021

## Abstract

Enuresis or bed wetting Is the most common cause of urinary incontinence and common group of disorders in childhood. That occur world-wide at approximately the same rate. 10% of all 7-yearolds, wet the bed at night and 2% to 3% during the day. Despite a high remission rate. The vast majority of elimination disorders are functional, Enuresis is associated with emotional distress in both children and parents, which is reversible once children become dry. We have about 20%-40% of all children with enuresis have additional, co morbid psychological disorders, not only externalizing conditions such as attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) but also internalizing disorders such as depression. These co morbid conditions require separate assessment and treatment – in addition to the symptom-oriented treatment of the child's elimination disorder. Most types of enuresis can be treated effectively with counseling and cognitive-behavioral approaches same of them may require additional medication involves pharmacology like desmopressin, imipramine and ant cholinergic drugs and conditioning alarm regimen .

## DEFINITION

as involuntary (or even intentional) wetting in children 5 years of age or older after organic causes have been ruled out [1]. The wetting must have persisted for at least three months A minmum of one episode a month be considered a disorder.[2]

Enuresis

Definition

Table C.4.1 Definitions according to the Children's Continence Society

| Symptom | Disorder |
|---|---|
| • Intermittent wetting during sleep<br>• Age 5 or more | Enuresis or nocturnal enuresis |
| • Daytime wetting<br>• Age 5 or more | Urinary incontinence or daytime urinary incontinence (not "diurnal enuresis"). In most cases functional. |

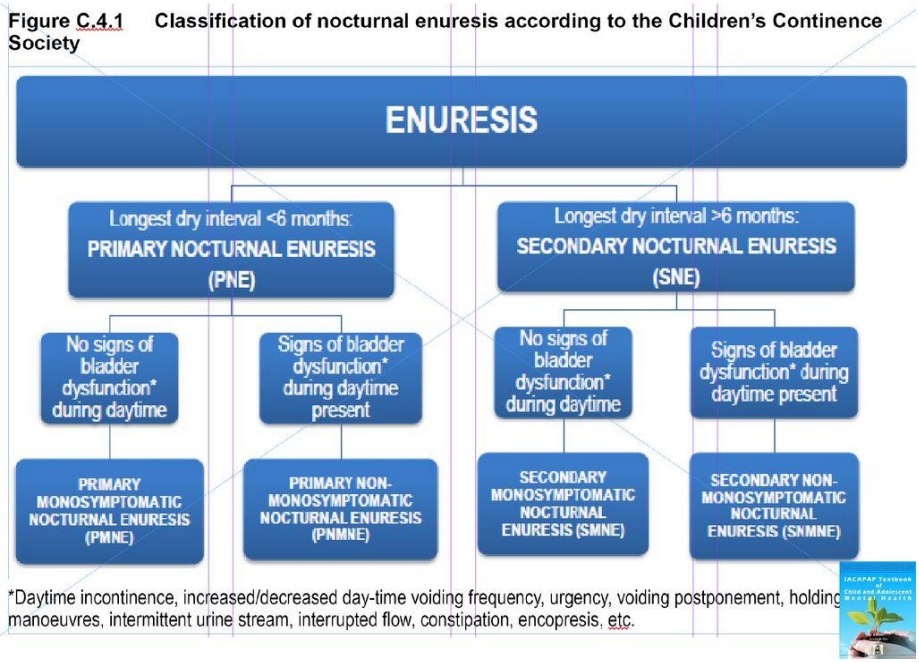
## Classification

Only two aspects need to be considered: the longest dry period and if lower urinary tract symptoms are present:

• *Primary enuresis* means that the child has been dry for less than 6 months (or not at all)

• *Secondary enuresis* means that a relapse after a dry period of at least 6 months has occurred for distinction is important because children with *secondary enuresis* have experienced stressful life-events (such asseparation of parents, birth of siblings, ...) more often , they have higher rates of co morbid psychiatric disorders [3]. These issues have to be considered in assessment and treatment, otherwise the treatment of primary and secondary enuresis is exactly the same. The presence of lower urinary tract symptoms is more important as it carries implications for treatment. Children who wet during sleep and do not have daytime symptoms suggesting disturbances of bladder function are suffering from *monosymptomatic* enuresis. Example they wet at night but bladder storage and emptying is completely normal (i.e., children go to the toilet 5-7 times during the day, do not postpone micturition with the use of holding manoeuvres, do not experience urge symptoms and can empty their bladders without problems). In these cases, treatment can focus on the wetting episodes during sleep without further preliminary procedures. Children who have lower urinary tract symptoms and may have gastrointestinal symptoms, such as constipation and soiling, have *nonmonosymptomatic* enuresis. And daytime symptoms have to be treated first before addressing the night-time wetting. The terms monosymptomatic and non-monosymptomatic are depend entirely on history and verified by voiding diaries

**Figure C.4.1 Classification of nocturnal enuresis according to the Children's Continence Society**




## EPIDEMIOLOGY

*Enuresis* is 2-3 times more common than daytime urinary incontinence.

_ Prevalence of night wetting decreases with increasing age: 20% in 4 year olds, 10% in 7 year olds, 1%-2%[4]

_in adolescents, and 0.3%-1.7% among adults [5]

_Frequent enuresis, defined by two or more wet nights per week, affected only 2.6% of them (boys 3.6%, girls 1.6%) [6,7]

_Primary is more common than secondary enuresis, with comparable rates at the age of 7 years , It is 1.5 to 2 times more common in boys than girls.{8,9}

_Monosymptomatic enuresis is twice (68.5%) as common as non-monosymptomatic enuresis (31.5%)

. The spontaneous cure rate of night time enuresis is 14% to 16% annually[10].

## CLINICAL PRESENTATIONS

The symptoms of *monosymptomatic enuresis* are _ deep sleep and difficult arousal , increased urine volume at night (polyuria) with large wetted volumes. The typical

presentation is a child who is extremely difficult to wake and who wets the bed with large amounts of urine. In contrast, bladder function during the day is completely normal. And the Children with a *non-monosymptomatic enuresis* have the same symptoms and in addition have signs similar to those with daytime urinary incontinence (except wetting). This means that some go to the toilet infrequently and postpone micturition with holding manoeuvres, others have signs of urgency and frequency, while others have to strain and the urine stream is interrupted, urinary tract infections (UTI's), constipation and encopresis are possible.
Children with *secondary enuresis* have higher rates of comorbid behavioural and emotional disorders ,A relapse can be precipitated by stressful life-events such as separation or divorce of parents Otherwise, they do not differ from those with primary enuresis

## ETIOLOGY AND RISK FACTORS

Genetic and neurobiological factors interact with environmental influences in the pathogenesis of elimination disorders. While some have a marked genetic component (monosymptomatic enuresis and urge incontninence), in others both genetic an environmental factors are involved (secondary enuresis), while some are mostly environmentally determined (voiding postponement).
Enuresis is a genetically determined maturational disorder of the central nervous system ( 70% to 80% of all children with enuresis have affected relatives. The concordance rates are higher among monothan di-zygotic twins. The recurrence risk for a child to be affected by enuresis is 40 % if one parent and 70 % if both parents had been enuretic . Most cases are consistent with with an autosomal dominant mode of inheritance; only one third of cases are sporadic . Several loci on chromosomes( 12, 13 and 22 )have been identified in linkage studies – irrespective of the type of enuresis{11,12} . A genetic predisposition for enuresis remains life-long and can be reactivated by risk factors, even in adulthood Children with enuresis have more neurological "soft signs" and need longer to complete motor tasks . In contrast, sleep architecture is not affected. Enuresis occurs in non-REM sleep phases, i.e. it is not associated with dreaming (enuresis during REM sleep is the exception). Enuresis occurs predominantly in the first third of the night – some children even wet the bed 10 minutes after falling asleep. The mean latency is 3 hours . This explains why some children with enuresis wet even during daytime naps

### Maturational delay

Since most cases of MNE resolves spontaneously a delayed maturation of a normal developmental process has been explored. Increased incidence of delayed language and slowed motor performances has been identified in some studies among children with enuresis{15}. Urodynamic and EEG findings have shown progressive maturation in bladder stability along with EEG changes suggesting increased central nervous system recognition of bladder fullness and the ultimate

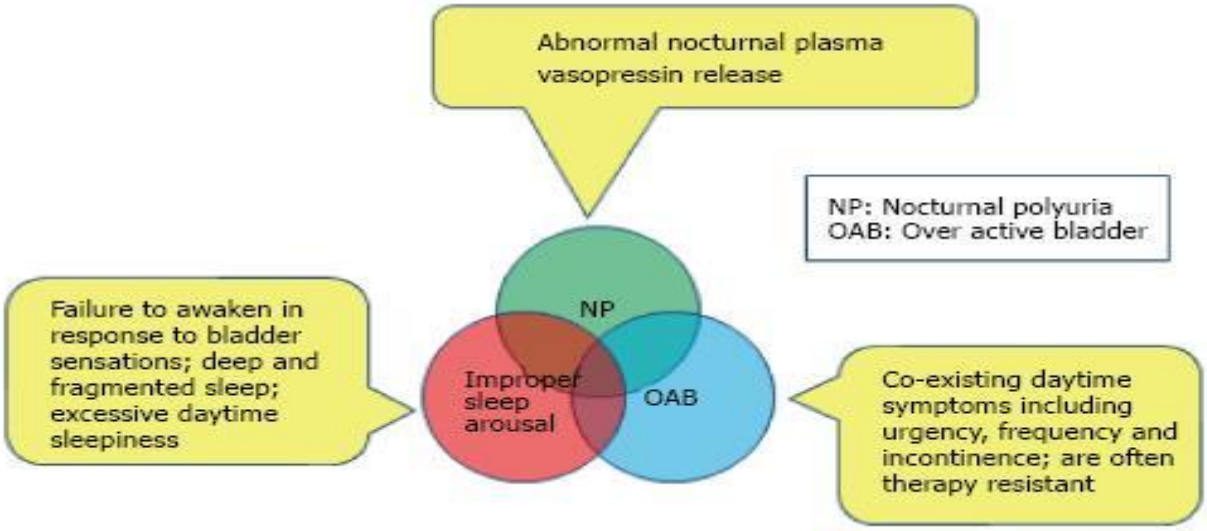
ability to suppress the onset of bladder contraction. Bladder capacity at birth is only around 60 mL and thereafter increases with age{16}. Children with nocturnal enuresis have been noted to have a smaller bladder capacity (functional rather than anatomical) even when there are no day time concerns{17}. There are reports of lower average height and lower mean bone age and late sexual maturation in enuretic than in non-enuretic children and adolescent. There is a greater incidence of enuresis in children who were delayed in the attainment of motor and language milestones as well. also Adverse event to medications as a side effect of a medication such as lithium, valproic acid, clozapine and theophylline (secondary enuresis). And Nocturnal polyuria Increased urinary output overnight might also play an important role in MNE{18}. The cause may include increased fluid intake before bedtime, reduced response to antidiuretic hormone, and or decreased secretion of ADH

## Psychosocial factors

modulate genetic and neurobiological risks in different ways. The time of initiation and intensity of toilet training has no effect on the development of enuresis. Psychosocial factors play a minor role in primary enuresis, the rate of psychological disorders and risk factors is not increased Children with secondary enuresis, however, have both higher rates of emotional and behavioral disorders as well as stressful life events prior to the relapse . The age of school entry (5-6 years) is the most common age for relapse while parental separation or divorce is the most important life event .

### The main mechanisms responsible for the development of enuresis are :

• Increased urine volume (polyuria) affects some but not all children. This is associated with a circadian variation (but not lack) of the antidiuretic hormone{23} .
• Impaired arousal is another important factor. In standardized waking schedules with sounds of up to 120 decibels, only 9% of children with enuresis can be woken up – significantly fewer than controls. This means that children with enuresis do not wake up when their bladder is full .
• Finally, children have an inhibition deficit of the pontine micturition centre of the brainstem. When the bladder is full during sleep, they are not able to sufficiently suppress emptying {24}.
In addition to local bladder dysfunction, the same factors are responsible for the development of *non-monosymptomatic enuresis*.




## How does nocturnal enuresis affect the child and family?

Nocturnal enuresis is socially stigmatizing and can affect quality of life and psychosocial wellbeing. Children report lower self esteem, which improves with successful treatment{26}, 36.7% of 9 year olds who were dry and 45.6% of children with enuresis ranked nocturnal enuresis as the eighth most stressful life event after items such as not having friends and being teased {27}. Their impaired health related quality of life is comparable to chronic conditions such as asthma and diabetes. Surprisingly, a child's perceived quality of life seems to be unrelated to the severity of enuresis but is associated with non-modifiable factors such as age, sex, and ethnicity{28}, with poorer quality for older children and those from culturally and linguistically diverse populations. Nocturnal enuresis can limit social opportunities, such as school camps and sleepovers, and it affects relationships with peers. Although 84% of children in a cohort study reported no problems with teasing, 48% indicated that their friends were aware of their enuresis, which caused them embarrassment {29}.Nocturnal enuresis presents a financial burden for families, with increased costs for laundry, disposables, and medical care.

# DIAGNOSIS

Assessment and a careful diagnosis are the bases for successful treatment – each subtype of enuresis and urinary incontinence responds best to its specific treatment . It is therefore advisable to take plenty of time for the first consultation with child and parents. with both background information and practical procedures can help . Most of the diagnostic process is based on simple, good clinical practice that can be delivered in most primary care settings. The most important step is a good and thorough history{30}. The history will lead the clinician towards possible diagnoses which need to be followed up and enable the exclusion of many other conditions.

## Frequency-volume chart

The second most important step is a 48-hour frequency-volume chart. Parents are asked to observe, record and measure over 48 hours when and how much their child voids and drinks, as well as associated symptoms such as incontinence, holding maneuvers, etc. Parents can be given a simple plastic measuring cup (which they will return at the next visit and that can be used many more times). This chart gives essential information for the diagnosis. In urge incontinence, for example, a micturition frequency of over 7 and small volumes (of 20-60ml) are typical; in voiding postponement, some children void only 2 or 3 times a day with large volumes of 400ml or more. Also, drinking habits can be assessed: most children with elimination disorders do not drink enough fluids (some only 400-600ml), while polydipsia is extremely rare. May parents are not aware of their child's voiding and drinking habits and will not be able to provide this information when asked.

## Questionnaires

Specific enuresis questionnaires are helpful to confirm and augment the information children and parents provide . The 48-hour volume/frequency chart, however, is far more important than a questionnaire

## . Physical examination

Each child should be examined physically at least once . It is essential that organic causes of incontinence are ruled out. A full pediatric and neurological exam is recommended. Children with daytime incontinence may require several examinations in the course of treatment, especially if UTI's and other complications occur. For most children with enuresis, especially with monosymptomatic enuresis, one exam will suffice {31}.

## Investigations

At least one urinalysis (with a urine stick) is recommended to be sure that no signs of bacteriuria and manifest UTI are present. This is especially important in daytime urinary incontinence; it is usually negative in children with monosymptomatic enuresis. If available, sonography is a very useful, non-invasive tool. In addition to the detecting structural anomalies of the urinary tract, sonography can give valuable information regarding three functional changes:

• A thickened bladder wall (> 2.5mm) can be indicative of a hypertrophy of the bladder wall as a sign of bladder dysfunction or it can be due to UTI's{33}

• Residual urine (>20ml) can be indicative of incomplete bladder emptying; and finally,

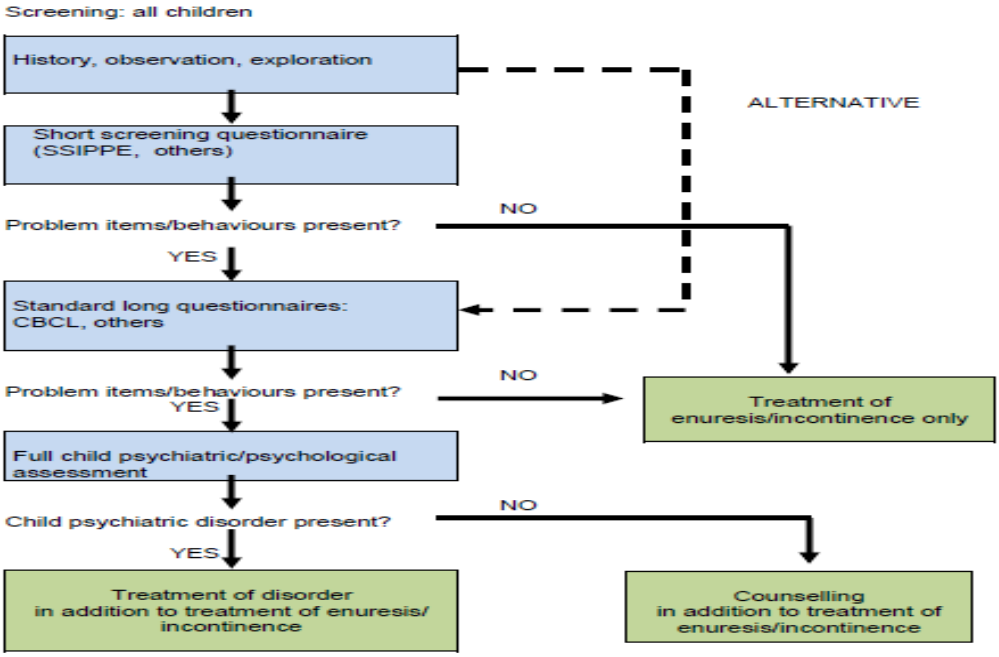
• An enlarged rectal diameter of more than 25mm can be a sign of stool retention and constipation.

However, even in Europe, sonography is not easily available in many countries In complicated cases with recurrent UTI's it is definitely indicated.

Uroflowmetry alone or combined with pelvic floor EMG is required for the diagnosis of dysfunctional voiding. So-called staccato (changes in flow rates) or fractioned (complete interruption of flow) are typical, combined with contractions of the pelvic floor. If not available, good clinical practice would be to listen and observe a child during the emptying of the bladder{32}: one can hear and observe the straining as well as the waxing and waning of the urine stream. All other, especially invasive, procedures should not be performed in children with enuresis or functional urinary incontinence unless they are absolutely indicated medically. Radiological and further urological investigations should be avoided as they are in most cases not necessary and can harm the child.

## Psychiatric assessment

In a child psychiatric setting, a routine assessment regarding comorbid emotional and behavioral disorders is recommended. In all other settings (paediatric, urologic etc.) at least a screening with a validated and standardized parental questionnaire is recommended because of the high frequency of comorbid disorders . This can be done in one or two stages, either by using a short screening questionnaire, such as the SSIPPE , first and a long questionnaire next, or by using a long questionnaire such as the CBCL . If many problem items are endorsed, a full assessment by a child psychologist or psychiatrist should follow{30}. If comorbid disorders are present, they should be treated



## Differential diagnosis

Somatic causes of urinary incontinence must be excluded. These include structural anomalies (such as epispadias, hypospadias, urethral valves, and other malformations of the urinary tract), neurologic conditions (such as spina bifida occulta, tethered-cord-syndrome, etc.) and other paediatric diseases (such as diabetes insipidus, diabetes mellitus). Comorbid emotional and behavioural disorders should be assessed in addition to the type of elimination disorder.

## TREATMENT

treatment of enuresis and urinary incontinence is based on simple, effective steps that can be delivered in many primary care settings. However, it is time-consuming as most interventions require cooperation of the child and parents. and Several meta-analyses have shown conclusively that, overall, non pharmacological interventions are more effective than medication

### General principles

Certain general principles should be followed for treatment:

• A child should be at least 5 years of age (the age required to diagnose enuresis and urinary incontinence), younger children do not require treatment

• Treatment should always be symptom-orientated, aimed at achieving continence (i.e., complete dryness){34}. Primary psychotherapy for enuresis is not effective and not indicated. Comorbid disorders should be treated separately according to evidence-based recommendations

• When there are several concurrent disorders, encopresis and constipation should be treated first because some children will stop wetting once these problems have been dealt with

• Daytime incontinence should be treated first, as many children will stop wetting at night once the daytime problems have been treated

• In non-monosymptomatic enuresis, all daytime bladder problems should be tackled first (according to the principles of urinary incontinence) before starting the specific treatment of enuresis.

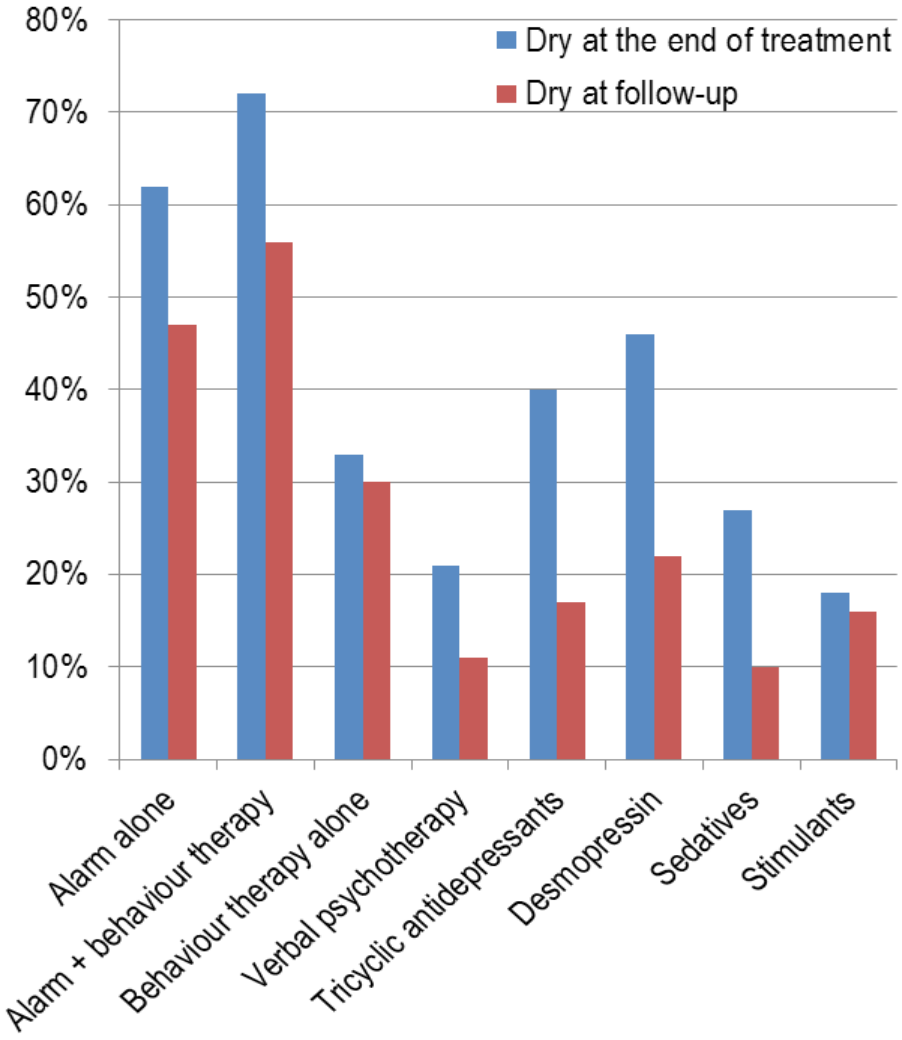
The initial treatment steps are simple, non-specific aspects of “good practice”:

• Counselling, support and provision of information.

• Enhancing motivation and alleviating guilt feelings.

• Educating about drinking and toileting habits: drinking more fluids during the day, taking time while on the toilet, sitting in a relaxed way, refraining from holding manoeuvres, etc.

• Discontinuing all ineffective measures such as punishing the child, fluid restrictions{35}, waking and lifting, ineffective medication, other alternative medicine treatments




A baseline period is then recommended with a simple observation and recording of wet and dry nights over a period of 4 weeks. Children are asked to draw a symbol for wet and dry nights (clouds and suns, stars, etc.) in a chart and bring it to the next consultation. . These simple measures will achieve dryness in 15-20% of cases without further intervention and are supported by evidence . If these simple interventions do not suffice, specific treatment is required. Two main interventions are available: alarm treatment and pharmacotherapy. As alarm treatment is more effective and has the best long-term results, this should be the first line treatment if child and parent are motivated.

, 62% of children are dry at the end of treatment and 47% at follow-up. conclude that “urine alarm treatments should not only be considered the treatment of choice, but the evidence from this review suggests that cure rather than management is a realistic goal for the majority of children suffering from nocturnal enuresis. “Alarm interventions are an effective treatment for nocturnal enuresis. Desmopressin and tricyclics appeared as effective while on treatment{36}, but this effect was not

sustained after treatment stopped and alarms may be more effective in the long run" . If alarm treatment cannot be implemented adequately, medication (desmopressin) is the second line treatment. If either method fails, a switch to the other treatment is recommended and was shown to be effective

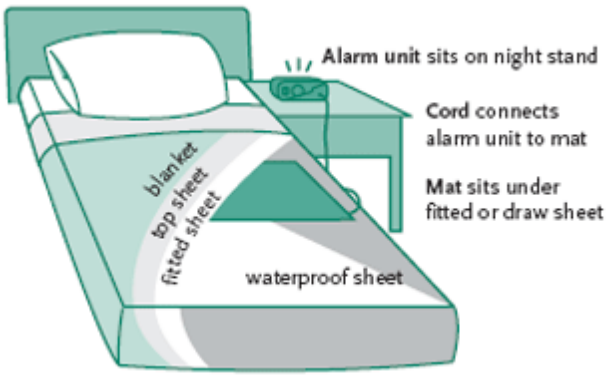
### *Alarm treatment*

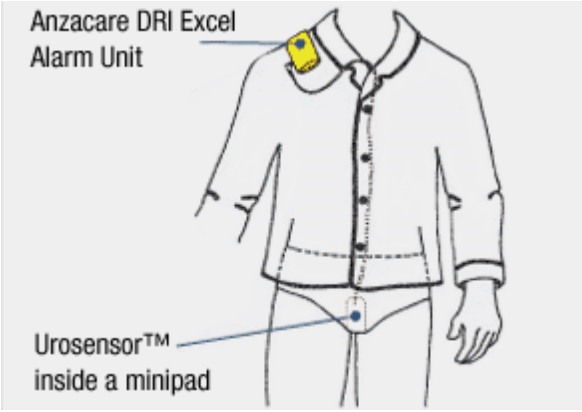
An alarm consists of a pad or a metal sensor, which is connected to a bell by a wire. Once the sensor becomes wet, an electric circuit is closed and the alarm is set off, they can be cleaned and used by different children many times over. Sterilization is not required, as urine is per se a sterile fluid (unless UTI's are present), cleaning with a surface disinfectant is enough. Two different types of alarms exist, body worn and bedside. In body worn alarms, the bell is attached to the night dress while the sensor is attached to the underpants. If desired, body worn alarms can be used with diapers. In bedside alarms, a metal foil or a cloth pad (with integrated wires) is placed under the top sheet of the bed and connected to an alarm next to the bed. Both alarms are equally effective{37}. Therefore, children should decide which alarm they prefer. The alarm should not just be prescribed but its functions demonstrated and shown directly during the consultation. Children should feel responsible for their treatment. Some instructions are extremely important and should be gone through in detail with parents and child:

1. Children are asked to go to the toilet before going to bed
2. The alarm is attached and switched on
3. In case of a dry night, nothing happens and the child can turn off the alarm the next morning. In case of wetting, the alarm is triggered and the child should wake up completely, either by themselves or with parental help
4. The child is asked to go to the toilet and urinate
5. The night dress and the bedding are changed and the alarm is reset.
6. The child should be actively involved in this process. If the child wets a second time during the night, the whole routine is repeated.
7. Parents are asked to record all relevant data in a chart

To be successful, the alarm must be used every night for a maximum of 16 week {2 22}. Some children become dry in only a few weeks, most will require 8 to 10 weeks and some a little longer. After 14 consecutive dry nights, use of the alarm is discontinued and the child is considered to be dry{38}. Parents are advised to restart alarm treatment if a relapse (two wet nights per week) happens, this occurs in up to 30% of cases.The alarm treatment relies on operant conditioning and should be enhanced with other measures including positive reinforcement with praise and other rewards, as well as aversive consequences such as getting up, going to the toilet and remaking the bed{39} . Dryness can be achieved by two basic mechanisms: either children learn to wake up and go to the toilet (one third) or they sleep through the night without wetting (two thirds). Usually, simple alarm treatment is sufficient. It can, however, be reinforced by additional means. A simple addition to the alarm is the so called "arousal training". In arousal training the alarm is set up before sleep, the alarm is triggered, children are instructed to turn off the alarm within three minutes, go to the toilet and reset the alarm{40}. If this is achieved

correctly children are rewarded with two tokens, such as stickers. If this is not achieved, one token has to be returned. In younger children, we found it advisable to modify this training: children receive one token if they are successful but do not have to pay back a token, which would be too frustrating for them. Arousal training has been shown to be more successful than alarm alone. A well-known training program is “dry bed training {41}. This is a complicated, difficult to perform program which starts with an intensive night (in which the child is awaken once every hour until 1 am) followed by maintenance treatment. Meta-analyses have shown that “dry bed training” is no more effective than alarm treatment alone. Therefore, it is not recommended. The combination of alarm treatment and desmopressin cannot be recommended due to conflicting results. However, if a child has urge symptoms (i.e., a non-monosymptomatic enuresis) a combination of ant cholinergic medication (for example 2.5mg to 5mg Oxybutinin or Propiverin at night) , otherwise the alarm may go off several times per night and the outcome will be less favorable.



## What are the options for medical therapy

### Indications for medication are:

- Unwillingness to undertake alarm treatment
- Lack of motivation in the children
- Family overwhelmed by demands such as a work situation, cramped housing, infants to care for, i.e., cooperation with alarm treatment is not possible
- Short-term dryness is required, e.g., for school outings.

Desmopressin has been used to treat nocturnal enuresis . It is a synthetic analogue of the pituitary hormone, arginine vasopressin, and it reduces urine production by increasing water reabsorption by the collecting tubules. Desmopressin was initially available as a nasal spray. Newer oral preparations (tablet or lyophilisate melt) have a lower risk for water intoxication than the nasal formulation{42}. Desmopressin is particularly effective for short term use when a rapid response is needed, when child is going for a sleepover or school camp. It is also useful when alarm training is difficult or contraindicated (when parents are not supportive), or in conjunction with other treatments in treatment resistant situations{43}. The drug is well tolerated—side effects (such as headaches, abdominal pain, and emotional disturbances) are uncommon. The rare but potentially serious side effect of water intoxication and hyponatraemia is minimised when children restrict drinking after taking desmopressin. It is advisable to withdraw desmopressin regularly (such as every three months) to assess the ongoing need. desmopressin (standard dose) had some effect during treatment in about 70% of children. Desmopressin is licensed for treating nocturnal enuresis in children over 6 years of age in more than 100 countries, although the nasal formulation was withdrawn for the treatment of this condition in 2007 because of a significantly higher incidence of symptomatic hyponatraemia compared with oral desmopressin {44}.

Desmopressin is taken in tablet form in the evenings only{45}. The oral dosage is 0.2mg to 0.4mg. It is advisable to titrate the required dosis over 4 weeks, . One starts with the low dosage of 0.2mg in the evening for two weeks. If the child is dry or a marked reduction of wet nights is documented one stays with this dosage. Otherwise, medication is increased
to 0.4mg in the evening. If children do not become dry with 0.4mg, they are considered to be non-responders and desmopressin is discontinued. Otherwise, one can continue with the required dosage for a maximum of 12 weeks, after which desmopressin should be stopped to check if the child can remain dry without medication. If a relapse occurs, desmopressin can be given for another 12 weeks and this regime can be continued for as long as indicated. Therefore it is important not to overdose and not to drink a large amount of fluids after taking the medication. Laboratory blood tests are not necessary.

Imipramine

Tricyclic antidepressants such as imipramine have a proven anti-enuretic effect{46} and similar relapse rates desmopressin. Mau be possible side effects of cardiac arrhythmias, hypotension, hepatotoxicity, central nervous system depression, interaction with other drugs even with therapeutic doses, a detailed family history, ECG before and during treatment and blood tests are recommended. A low dose of 10mg to 25mg in the evening (1mg per kg of body weight per day or less) is often sufficient. If higher doses are necessary, imipramine should be give 3 times a day and the medication slowly increased to a maximum of 3mg per kg of body weight per day. Due to side effects (and toxic effects in case overdosage), imipramine has become a third line treatment for severe therapy-resistant cases.

**Anticholinergic drugs**

Ant cholinergic drugs have a potential role, mainly in non-monosymptomatic nocturnal enuresis. They are thought to act by treating the underlying overactive bladder, thereby increasing the storage capacity of the bladder. Although ant cholinergic monotherapy is ineffective, it can improve treatment response when combined with other established treatments, such as imipramine, desmopressin, or enuresis alarms, particularly in treatment resistant cases.{47 }, and oxybutynin combined with imipramine was superior to imipramine monotherapy, with improved treatment response{48} .and oxybutynin combined with desmopressin was superior to desmopressin monotherapy in refractory monosymptomatic nocturnal enuresis{48}. ant cholinergic drugs (tolterodine, solifenacin, propiverine) have fewer side effects{49}, with variable efficacy compared with oxybutynin,{47_49}.

## Psychological treatments

Because children with nocturnal enuresis have an increased risk of behavioral or psychological disorders, psychological treatments have a role in enuresis, particularly in the presence of treatment failure and comorbid disorders. ICCS recommends psychological screening of children with nocturnal enuresis using validated parental questionnaires. When marked symptoms are present, a full child psychological or psychiatric assessment is rec ommended. If a behavioural or emotional disorder (such as attention-deficit/hyperactivity disorder) is diagnosed according to ICD-10 (international classification of diseases, 10th revision) or DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) criteria, evidence based counseling and treatment are recommended. The NICE guideline concludes that there is no evidence to justify the cost of psychotherapy for enuresis if no clinically relevant psychological disorder is present. The main treatment goal in these cases is symptom oriented treatment of enuresis only. NICE recommends treating co morbid disorders, because this is thought to help improve adherence to the enuresis treatment.

## What is the prognosis for nocturnal enuresis

According to large epidemiological studies, nocturnal enuresis decreases with age, with a spontaneous remission rate of about 15% per year. A large study found that

children with more severe forms of enuresis and those with non-monosymptomatic enuresis are more likely to have persistent problems, and treatment for these children should not be delayed. Importantly, nocturnal enuresis can improve with treatment, and improved self esteem and quality of life have been reported after successful treatment. It is therefore important to offer timely treatment, and to refer children for specialist care when treatments are not effective

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