This guide tries to answer questions about PMNE (primary monosymptomatic nocturnal enuresis) in children. It has been structured in different chapters where evidences have been searched systematically. The authors used the level of evidences and degree of recommendations following the Center for Evidence Based Medicine, Oxford (annex 1).

Prevention

Most children develop normal urinary functioning and continence irrespective of the timing and type of toilet training undertaken. However, if delayed or if inappropriate, incomplete voiding is prolonged and this abnormal functional behavior can persist and predispose to urinary tract infections, dysfunctional voiding, and overactive bladder **[IIc]**.

The following attitudes have been shown to be beneficial in achieving daytime urinary continence at an earlier age and avoiding dysfunctional voiding. Although it is not known if they will also bring about the onset of nocturnal urinary continence, it is recommended **[C]**:

- Start toilet training before the age of 18 months, perhaps when the child is able to wake up dry from his/her nap
- Use of a pot or potty chair that properly supports his/her thighs and feet.
- Suggest to the child that they should urinate when you see or imagine that they feel the urge, so that they can do so on the first try. Do not keep the child seated on the pot until he/she urinates and do not insist that they strain if the first attempt fails.
- Be persistent in this training, because the objective can be achieved in less than three months. Do not dilute the effort by continually changing the technique.

Associated factors

Table II

There is an association between chronic headache and nocturnal enuresis, albeit none of the studies is specific to PMNE. Enuresis is approximately twice as frequent in children with chronic headache (headaches that are so frequent as to interfere with their daily activities for a period of at least 6 months) than it is in controls (OR = 1.8; 95% CI: 1.1-2.9) **[IIb]**.

It is recommended inquiring about chronic headache in children with nocturnal enuresis **[B]**.

Despite the fact that wetting incidents have been described as the manifestation of nocturnal epileptic fits, no evidence has been found of epilepsy as an associated factor to nocturnal enuresis **[IIIb]**.

Table II. *Factors associated with primary monosymptomatic nocturnal enuresis*

Primary monosymptomatic nocturnal enuresis

Associated	Not associated
Chronic headache [IIb] (OR = 1.8; 95% CI: 1.1-2.9)*	Epilepsy [IIIb]
Attention deficit hyperactivity disorder [IIIb] (OR = 6.0; 95% CI: 2.5-14.3)*	Psychological problems in general [IIb
Patients with prior failures or have been referred to hospital have low self-esteem [IIIa]	Sleep disorders. Signs that they have a harder time waking up [IIIb]
Detrusor overactivity [IV], particularly in persistent enuresis and treatment failures	Urinary tract infection/bacteriuria [IIc]
	Diabetes mellitus [IV]*

Association is not well established

Sleep apnoea syndrome [IV]*
Asthma/allergy [IV]*
Caffeine
Encopresis/constipation [IV]*
Diabetes insipidus
Pinworm (Enterobius vermicularis) infestation [IV]*

* The studies evaluated do not address PMNE exclusively.

An electroencephalogram is not justified in the assessment of nocturnal enuresis **[B]**.

Children with untreated ADHD have a 6-fold risk of suffering enuresis than controls (OR = 6.0; 95% CI: 2.5-14.3). This risk persists, albeit to a lesser extent, in a group of children who have already been treated **[IIIb]**.

Given the high prevalence of these two conditions and their association, it is clinically important to know if there is concomitant ADHD in enuretic children. Hence, ADHD symptoms in children that present enuresis should be investigated **[B]**.

There is no association between psychological problems in general and PMNE, although there is with secondary NE [IIb]. However, children with PMNE seeking treatment, who have had previous failures, or have been referred to hospital have low self-esteem **[IIIa]**. Treatment of enuresis enhances the child's self-esteem in the short term regardless of outcome **[Ib]**.

Early treatment of enuresis is recommended in Primary Care to improve **[A]** or prevent low self-esteem**[D]**.

PMNE is not associated with any sleep disorder, although there are signs indicating that these children find it more difficult to wake up, at least as a result of acoustic stimuli **[IIIb]**.

Although waking up plays an important role in the pathogenesis of enuresis, no clinical implications have been found. Sleep patterns need not be studied as part of the clinical history of a child with enuresis **[B]**.

Only cases and case series have been described of the association of sleep apnoea syndrome and nocturnal enuresis [IV]. None of them evaluate PMNE specifically. An association has been demonstrated with secondary enuresis [Ib].

It is recommended obtaining a history of sleep apnoea symptoms in children with PMNE, despite the fact that the level of evidence is low **[C]**. It should always be ruled out in cases of secondary enuresis **[A]**.

The association between asthma/allergy and enuresis is not conclusive. Existing studies are of poor quality and contradictory, and none of them are specific to PMNE **[IV]**.

It is not recommended specifically investigating the presence of asthma/allergy in children with PMNE **[C]**.

Although it has never been studied, it is reasonable to recommend that caffeine-containing beverages be avoided late in the evening given their diuretic effect **[D]**.

Although there is a clear association between constipation/encopresis and secondary enuresis, its relationship to PMNE is not well established **[IV]**.

The presence/absence of constipation or encopresis is worth investigating in all patients with enuresis; if present, treat the constipation first **[C]**, since constipation is easy to diagnose on clinical grounds (fewer than 3 bowel movements per week), and given the possibility that constipation can be the cause of enuresis.

There is insufficient evidence available to confirm that pinworm infestation is associated with NE **[IV]**.

At present, and in our setting, Graham's technique is not justified in all children with PMNE **[C]**.

Most protocols or guidelines recommend ruling out urinary tract infection or bacteriuria in children with enuresis. However, there is evidence that PMNE is not associated with urinary tract infection/bacteriuria **[IIc]**.

In PMNE, it is recommended adopting the same attitude to urinary tract infection/bacteriuria as in the general population **[B]**.

Juvenile diabetes mellitus is not associated with PMNE, although it is associated with secondary enuresis **[IV]**.

It is not recommended routine testing to rule out diabetes mellitus in children with PMNE **[C]**.

There is no evidence of an association between diabetes insipidus and NE.

It is not recommended routine testing to rule out diabetes insipidus in children with PMNE **[D]**.

There is evidence that bladder hyperactivity is associated with PMNE, particularly in cases where treatment with desmopressin or alarm fails **[IV]**.

The usefulness of anticholinergics in PMNE should be evaluated in clinical trials **[C]**.

Diagnosis

It is recommended actively searching for cases from 5 years of age in any visit for illness or routine check-up **[D]**.

The bladder diary is a method that assesses several parameters that help us to make an accurate diagnosis of "monosymptomatic" enuresis and to assess prognostic values such as MDVV (Maximum Daytime Voided Volume) **[Ia]**, which will guide us in our decisions: the type of treatment to follow or whether to refer to other specialists.

It is essential that the bladder diary be filled in for at least 3 days [A]. It can be done conveniently over two weekends.

In monosymptomatic nocturnal enuresis it is recommended adopting the same attitude to urinary tract infection as in the general population **[B]**.

There are no studies that assess the prognostic impact the existence of bacteriuria at the time of diagnosis of PMNE has. Nevertheless, in studies on

enuresis treatment failure or persistence into puberty or adulthood, no higher prevalence of bacteriuria is found **[IV]**.

It is not recommended routine testing to rule out urinary tract infection **[B]**, diabetes mellitus **[C]**, or diabetes insipidus **[B]** in children with PMNE.

Abdominal ultrasound, plain abdominal or spinal x-rays, or other examinations are not needed in PMNE.

Simple behavioural interventions

This includes:

- Restriction of fluids and diuretic drinks in the evening and at night.
- Waking the child up during the night.
- Waking the child up according to a schedule.
- Motivational therapy with charts.
- Bladder training by toileting schedule.
- Bladder training by mid-stream urine interruption.

There are no good quality studies that evaluate the efficacy of simple behavioral intervention in PMNE.

Bladder retention training by toileting schedule does not provide any benefit in PMNE; hence, it is not recommended in Primary Care **[B]**.
There are no data available that evaluate the efficacy of bladder training by mid-stream urine interruption and it is not recommended its use in light of the fact that it can predispose to dysfunctional voiding **[D]**.
Despite the lack of quality PMNE data, motivational therapy using charts with stars, drawings… helps to objectify the baseline situation regarding the number of wet nights and can be recommended before and together with other treatments, since it lacks adverse effects **[D]**.

Complex and educational behavioral interventions

These include:

- Dry bed training.
- Full spectrum training at home.
- Other complex alternatives.
- Educational interventions: informational brochures or CDs.

There are no data that demonstrate that any complex behavioral intervention is efficacious or effective **[IIb]**.

Information, although it is useful in

teaching children some of the concepts involved in enuresis, has no therapeutic effect regardless of whether it is presented in the form of brochures or in multimedia format **[IIIb]**.

Given the scant efficacy of complex and educational interventions, it is not recommended their use in Primary Care **[B]**.

Alarm

Alarm intervention is more efficacious than no treatment at all. The relative risk of achieving cure, i.e. 14 dry nights without relapse, is 5.56 times greater with alarm therapy than with no treatment (RR = 5.56; 95% CI: 1.54-20.00 and NNT = 3; 95% CI: 2-8) **[IIb]**.

Alarm intervention is a treatment option for PMNE if the family is motivated and collaborative **[B]**.

There is no evidence of clinical trials that compare the outcomes of simple or complex behavioral intervention with the alarm system in children that present only PMNE.

The association of behavioral intervention (dry bed training or bladder training) with alarm therapy does not provide any advantage over alarm therapy alone **[IIb]**.

There are no clinical trials that evaluate the association of alarm therapy with other simple or complex behavioral intervention techniques in children with PMNE.

It is not recommended associating bladder retention training by toileting schedule techniques or dry bed training with alarm therapy **[B]**.

Although not specifically evaluated in children with PMNE, the reinforcement technique (prolonging treatment by administering extra fluids before going to bed once the treatment objective has been attained) lowers the relapse rate in children with nocturnal enuresis **[Ia]**.

The reinforcement technique should be recommended before completing alarm therapy in children with PMNE **[B]**.

It is recommended a change in treatment if, once alarm treatment has begun, the child never wakes up **[C]**. It is recommended monitoring this response over a minimum period of one month **[D]**.

There is not enough evidence to decide that one alarm system is better than another in children with PMNE **[Ib]**.

Modern portable alarms are safe and well-tolerated **[Ia]**.

Desmopressin

When the objective is complete dryness, the pooled analysis of two studies showed that in children who were heavy bedwetters (more than 3 wet nights per week), the 0.4-mg dose was 1.14 times more likely to achieve 14 consecutive dry nights than placebo (RR = 1.14; 95% CI: 1.05-1.23) **[IIb]**.

Drug treatment with desmopressin is a therapeutic option in PMNE **[B]**.

Dose/response data do not reveal any differences in decreasing wet nights between doses of 20 µg and 40 µg administered intranasally **[IIb]**; although when administered orally said reduction is dose-dependent **[Ib]**.

If the objective is to achieve initial success (14 consecutive dry nights), there are no differences between the oral doses of 0.2, 0.4, and 0.6 mg **[Ib]**, although the sample size in the studies is insufficient to confirm effect differences among the doses.

Because the optimal dose of desmopressin is yet unknown, whether orally or intranasally administered, it is recommended customizing treatment to the minimum effective dose (0.2-0.4 mg oral and 10-40 µg intranasal). There are two trends: 1) to begin treatment with the minimum dose and titrate up if the response is insufficient, or 2) start directly with the higher dose, which can subsequently be titrated down, although there are no data that provide guidance as to when to do this **[D]**.
Intranasal desmopressin should be administered at bedtime. Because orally administered desmopressin has its onset of action 30 minutes post-administration, it is recommended that it be taken 30 minutes before the last void and going to bed **[D]**.

Despite the fact that comparative studies of the oral route versus the intranasal mode of delivery have not been powered to confirm non-inferiority of both routes, an oral dose of 0.2-0.4 mg is used in both clinical practice and research as the equivalent to an intranasal dose of 20 µg **[IIb]**.

In a comparative study with alarm treatment, the effect of desmopressin was already apparent in the first week of treatment **[Ib]**, although the maximum effect of fewer wet nights was seen at week 4 **[Ib]**.

Desmopressin is a safe drug, both in the short and the long term. Adverse effects are not very common and even less when administered orally **[Ia]**.

To prevent water intoxication, it is recommended limiting fluid intake the evening that desmopressin is taken, to no more than 240 ml (1 glass of water) since 1 hour before to 8 hours after **[D]**.

Without taking cost-effectiveness studies into account, the oral mode of delivery is recommended because it is safer **[A]** and easier to administer, which improves treatment compliance **[D]**.

Prolonging treatment with desmopressin beyond 1 month does not improve outcomes in terms of complete dryness or cure **[IIb]**. Maintained efficacy has been observed without side effects in treatment periods of up to 5-7 years **[IIb]**.

If the objective is to cure the condition, discontinuation should be started one month after attaining initial success **[B]**. In case of prolonged treatments, it is recommended withdrawing therapy periodically for 1-2 weeks in order to re-evaluate **[D]**.

Relapse is common in children with enuresis if treatment with desmopressin is discontinued abruptly **[Ia]**.

It is not recommended precipitous interruption of treatment with desmopressin that is achieving good response **[B]**.

There are no quality studies that demonstrate that withdrawal with progressively decreasing doses prevents relapse.

A program of structured withdrawal (gradual, intermittent at full doses) achieves cure without relapse in over half the patients that have previously relapsed without this regime **[IIb]**.

It is recommended using a structured withdrawal plan (at full doses) when finishing treatment with desmopressin **[B]**.

Association with other treatments

The association of desmopressin with alarm therapy offers no long-term advantages, although it does achieve more dry nights initially **[Ib]**.

Except for specific situations in which there is great interest in achieving a higher rate of dryness at the beginning of treatment, it is not recommended routinely associating desmopressin and alarm **[A]**.

In the case of children who wet the bed more than once per night, the use of desmopressin might be recommended with the aim of decreasing the number of nocturnal voids to just one, to make alarm therapy more tolerable **[D]**.

The association of desmopressin with anticholinergics might achieve a higher response rate than desmopressin in monotherapy, particularly in patients with prior treatment failure **[IV]**.

There is not enough evidence to recommend the association of anticholinergics, although it might be an alternative after treatment failures **[D]**.

Strategy with alarm therapy following desmopressin failure

In children with PMNE who do not respond initially (in 1-2 months) to desmopressin, associating alarm therapy does not lead to better long term outcomes (4 months) than alarm therapy alone **[Ib]**.

It is recommended not associating alarm therapy to desmopressin in children who have not responded to desmopressin **[A]**.

Advantages and disadvantages of different treatments

(Table III)

In children with PMNE, desmopressin acts faster and is more effective than alarm therapy in the short term (1 week) **[Ib]**. Long term (3-6 months), both treatments are equally effective during active treatment **[Ia]**. In contrast, when treatment is discontinued, there are fewer relapses with alarm therapy **[Ib]**.

When the treatment objective is dryness in the short term, it is recommended desmopressin and not alarm therapy **[A]**. If the aim is to maintain dryness without relapses when concluding treatment, alarm therapy offers obvious advantages over desmopressin **[A]**.

Prognostic factors of treatment response

(Tables IV and V)

Alarm therapy requires a great effort and collaboration by the child and his/her family. The parents' or child's concern and motivation with respect to bedwetting are favorable predictors to start alarm therapy, while parental intolerance predicts a high dropout rate with alarm therapy, but does not influence pharmacological treatment **[Ib]**.

It is recommended not starting alarm treatment if low motivation is detected in the family or the child **[B]**. In this case, desmopressin is the treatment of choice **[B]**.

There are no studies of prognostic factors for behavioral interventions other than alarm therapy.

Generally speaking, we can state that prior treatments for enuresis do not influence the response to a therapy with an alarm system or with desmopressin. However, the studies that evaluated this factor do not report compliance with previous treatments, their duration, or the time elapsed since they were completed, hence, one must be cautious when interpreting these data **[Ib]**.

Many wet nights/week is a predictive of a good response to alarm therapy **[IIa]**.

Table III. *Advantages and disadvantages of the different treatment options*

	Advantages	Disadvantages
Simple behavioral therapy	– Easy to implement – Safe – Improves motivation and is complementary to other treatments	– Low cure rate
Alarm	– Low relapse rate – Safe	– Slow response – Requires collaboration of the child and his/her family – Non-reimbursable by the Spanish National Health Service
Desmopressin	– Fast response – Does not require collaboration of the child or of his/her family. – Reimbursable by the Spanish National Health Service – Safe	– High relapse rate – Restriction of fluid intake at the end of the day

Alarm therapy is a good treatment option when there is a high frequency of wet nights **[B]**. Based on the data in the literature, it is not possible to establish a precise number that defines "high frequency of wet nights", although it has been observed that the greater the number of wet nights, the better the response.

In contrast with alarm therapy, having fewer wet nights prior to initiating treatment is a positive predictor for treatment outcome with desmopressin **[Ib]**.

Young children (6-7 years of age) with PMNE with few bedwetting incidents (1-2 times/week) show an excellent response to desmopressin **[IIb]**.

Desmopressin is a good treatment option when there are few wet nights **[B]**, even in young children **[B]**.

There are no studies that evaluate the factor of the number of wetting incidents per night for alarm therapy. The number of wetting incidents per night does not influence treatment with desmopressin **[Ib]**.

MDVV < 45% of the predicted volume for the child's age, according to Kof-

f's formula [theoretical MDVV in ml = (age + 2 years) x 30] is a poor prognostic factor for alarm therapy **[IV]**.

When the MDVV is ≤ 75% of the predicted level for the child's age, the probability of response to desmopressin is 3.54 times lower (RR = 3.54; (95% CI: 1.81 to 6.90) **[Ib]**.

It is recommended determining MDVV by filling in bladder diaries **[A]**, do not administer desmopressin in children with a MDVV less than 75% of the amount calculated by Koff's formula **[B]** and refer the child to the urologist if this volume is less than 45% **[C]** because it is a poor predictor for response to both treatments (desmopressin and alarm).

Stressful situations in the child or his/her family, delayed development, and psychiatric problem(s) in the child are prognostic factors of poor response to alarm therapy **[Ib]**.

ADHD is a factor of poor prognosis for alarm therapy; however, does not influence drug treatment **[IIb]**.

In children with enuresis and the suspicion or diagnosis of ADHD or a psychiatric condition, it is recommended starting treatment with desmopressin instead of alarm **[B]**.

The observation of errors when performing the Rey-Osterrieth complex figure test is considered a poor predictor of response to desmopressin. Two or

Table IV. *Predictive factors for alarm therapy*

Favorables	Unfavorable
– Motivation (parents and child are concerned) [Ib] – Many wet nights/week	– Parental disapproval of enuresis [Ib] – Maximum daytime voided volume < 45% [IV] – Stressful situation of the child and family or a psychological disorder in the child [Ib] – Attention deficit hyperactivity disorder [IIb]
No influence	
– Gender [Ib] – Age [Ib] – Previous treatments [Ib]	– Demographic factors [Ib] – Social class [Ib] – Adverse architectural elements in the home [Ib]

Table V. *Predictive factors for treatment with desmopressin*

Favorables	Unfavorable
– Low number of wet nights/week [Ib]	– Maximum daytime voided volume 75% [Ib] – Errors in copying or reproducing Rey-Osterrieth complex figure test [Ic] – Hipercalciuria nocturna [IV]
No influence	
– Gender [Ib] – Family history of bedwetting [Ib] – Parental disapproval of enuresis [Ib] – Number of wetting incidents per night [Ib]	– Attention deficit hyperactivity disorder [IIb] – Motivation (parents and child are concerned) – Previous treatments [Ib] – Demographic factors [Ib] – Urinary osmolarity [Ib]

more errors in copying and reproducing the figure by heart (RR of success = 0.35; 95% CI: 0.20-0.61) or more than 1 error when only reproducing by heart is done (RR of success = 0.44; 95% CI: 0.29-0.66) **[Ic]**.

Given the complexity of the test (time consuming and difficult to interpret), we do not consider it to be helpful in clinical practice, and therefore do not recommend its use in Primary Care **[D]**.