10. Treatment

Involuntary micturition while sleeping (without other associated problems) is not a problem in itself in young children because parents expect it, as do both the family in general and society. When the child grows up, he/she is expected to learn to keep the bed dry without help or with gentle encouragement from the family.

If this does not happen, then the problems arise:

- For the child: embarrassment, social limitations, diminished self-esteem.
- The parents: irritation, concern, shame, expenses, and social constraints.

Treatment is motivated by the desire to avoid these problems.

Systematic review

In order to analyze the best available evidence on the treatment of PMNE, we have taken into account the clinical studies that were published and selected in the latest update of the Cochrane Review. Subsequent to that date, we have conducted searches as indicated in 'Materials and methods'.

Clinical trials on enuresis are scarce; most of them are hospital-based, and many are of poor methodological quality, even some of those that were selected in the Cochrane Review. Perhaps that is why the authors of the Cochrane Review have been forced to group clinical studies of children with different inclusion criteria (monosymptomatic and non-monosymptomatic enuresis, with or without other associated symptoms, different treatment duration and success criteria...) in order to have enough data to conduct meta-analyses and compare different treatments. This requires that the outcomes be interpreted cautiously when extrapolating them solely to PMNE. Therefore, and with the aim of selecting only those studies/trials that adapt best to the subject at hand (despite the fact that this may have led to the odd study being omitted), we have selected only those articles that claim to meet the following characteristics:

1. Controlled, randomized or quasi-randomized clinical studies on the treatment of enuresis.

2. Treat children or adolescents (see selection criteria).
3. Deal with primary nocturnal enuresis and have ruled out organic causes and daytime urinary incontinence.
4. Report baseline data regarding wet nights.

What is the treatment objective?

The data published on treatment outcomes are not always easy to compare because the results vary on the basis of the success criteria used. Given that just a not-too-demanding criterion can improve results considerably, comparing one treatment with demanding criterion with another one having less demanding criterion is deceiving. We comment on the different response criteria observed in the literature below:

- Initial success: 14 consecutive dry nights.
- Complete dryness: 100% response. The only valid response in older children.
- Complete response: > 90% response versus baseline. (Examples: if the child wets the bed 5 nights per month, then wetting less than 1 night every 2 months. If the child wets 5 days/week at baseline, then wetting fewer than 2 nights per month). Clinically, this can be considered close to success in small children.
- Partial response: >50 - 90% response versus baseline. Although it refers to a treatment action and can serve as a measure of treatment efficacy at an experimental level, it is not clinically relevant because if a child wets the bed every night, there is no point in him/her going to camp and wetting 50% of the days, for example.
- No response: < 50% response versus baseline.

Clinically valid treatment objectives are:

- Cure: once treatment has been completed, the child "should not wet the bed", either because he/she does not get up or because he/she wakes up and goes to the toilet (nocturia) [initial success or complete dryness without relapses during follow-up].
- Reliable control for special situations: faced with an event such as a visit to a friend's house or going to camp... the child needs to be sure that he/she "will not wet the bed" for a few days [initial success or complete dryness].
- Impact reduction: In the event of poor response to prior treatments,

a poor prognosis for different reasons, problematic situations that prevent initiation of curative treatment [complete dryness without relapses]... we would be content if the child "doesn't wet the bed" maintaining long-term treatment (months or years) to avoid the negative consequences [complete dryness or complete response].

From the clinical standpoint, the only acceptable response would be initial success and complete dryness[92] (the main treatment objective) or a full response (acceptable in certain situations, particularly in small children, palliative situations, and unacceptable in others). 'Partial response' and 'No response' should always be considered treatment failures.

In our review, we find that almost all the studies have opted for short, pre-treatment observation periods (usually 2 weeks), which means that the heavy bedwetters must be selected in order to obtain sufficient wet nights to calculate a percentage response with sufficient accuracy, and this already introduces a bias.

It is clear that the observation period should be longer in children that do not wet frequently (at least 1 month).

10.1 How efficacious are behavioral interventions?

A. Simple behavioral intervention

Traditionally, nocturnal enuresis was treated with simple therapies aimed at decreasing nocturnal diuresis or modifying nocturnal voiding behaviors, including:

- Restriction of fluids and diuretic drinks at the end of the day.
- Getting the child out of bed at night to urinate, even when he/she is asleep.
- Waking the child according to a schedule with an alarm in order to void.
- Motivational therapy using charts with positive symbols when the bed remains dry, e.g. stars or suns, and negative symbols when it is wet, e.g. dark clouds.
- Bladder retention training by toiletting schedule: voiding control to increase the functional capacity of the bladder through exercises such as progressively delaying micturition for longer periods of time or drinking large amounts of fluids.
- Bladder training by mid-stream urine interruption: intermittent closing exercises of the striated urethral sphincter during micturi-

tion. Hindering bladder emptying predisposes to dysfunctional voiding. This technique should not be used to treat PMNE. When required, it is recommended pelvic floor muscle strengthening to make the patient aware of the mechanism that activates these muscles. Once the technique has been learned, the individual should perform the exercises, but not while voiding.

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

Restriction of fluid intake is a logical intervention for nocturnal enuresis that is generally recommended by doctors, albeit it has not been proven to be effective. Avoiding caffeinated drinks, which are diuretic, is a reasonable recommendation, although it has not been the object of study.

We only found 4, low quality clinical studies that only analyze *bladder retention training by toiletting schedule*. One[93], a very poor quality study, included only 9 patients per group and a short follow-up period of 5 weeks, and detects no differences between bladder retention training and the waiting list.

Bladder retention training by toiletting schedule does not improve the course of the disorder when used together with alarm therapy[94,95] [IIb].

This same technique, used as the sole treatment in heavy bedwetters, attained similar outcomes to those achieved after completing treatment with desmopressin[96] [Ib]. For twelve weeks, 114 frequent bedwetting children were treated with desmopressin or bladder retention training once a day to increase voided volume. Despite the fact that the desmopressin-treated group had considerable fewer wet nights compared with the bladder retention group, no differences were observed after treatment completed. Both groups achieved the objective of "great improvement" with the same frequency (RR = 1.25; 95% CI 0.97-1.62) and the number of relapses in patients presenting "great improvement" was unchanged (RR = 0.92; 95% CI 0.81-1.05).

Bladder retention training by toiletting schedule does not provide any benefit in PMNE; hence, it is not recommended in Primary Care **[B]**.

There is no evidence from clinical studies that assess other simple behavioral techniques in PMNE. The Coch-

rane Review meta-analysis examines all nocturnal enuresis, including those studies in which daytime urine losses have not been ruled out. Although it considers that more studies are required, its conclusions are: Motivational therapy with charts (stars, drawings…), getting the child out of bed and waking him/her according to a given schedule slightly improve both the number of dry nights and the number of children that are cured and reduce the number of relapses compared with different controls.

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]**.

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]**.

B. Complex and educational behavioral interventions

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

Within behavioral therapies aimed at changing nocturnal enuresis behavior, there is a group called "complex therapies". It was located the evidence about:

- Dry bed training.
- Full spectrum home training.
- Other possible interventions.

Educational interventions have also been sought.

Very few studies have been found in children with PMNE, and those that do exist are of poor quality.

Dry bed training was developed in the 1970s for use in adults with learning problems. It is a very complex technique to implement, and basically consists of getting the subject up out of bed. The first night, once every hour to go to the toilet, and if he/she wets the bed he/she is 'punished' for 45 minutes by having to clean the bed. During the following nights he/she is awakened once. Certain modifications have been introduced to make it more bearable.

Full spectrum home training: this technique combines alarm therapy with cleaning, bladder control training, and reinforcing what has been learned by

drinking extra amounts once bladder control has been achieved. Alarm therapy is maintained until the first 14 dry nights are achieved.

Other interventions include counseling, psychotherapy, and complementary medication. There are no data to support these alternatives.

As far as *educational interventions* are concerned, different methods of providing information for children and parents have been studied.

Four clinical studies are available, one of them quasi-randomized that only analyzes dry bed training; there is another on educational intervention.

One trial[97] [IIb] compares three methods of conducting dry bed training with a waiting list. There are no data for the control group following 5 weeks. The number of dry nights per week is similar in all the groups. The cure rate between the intervention and control groups cannot be compared.

Three trials compare dry bed training as add-on treatment to alarm therapy versus alarm therapy alone, with small sample sizes and very different outcomes. Azrin[98] finds advantages with behavioral therapy, albeit the study only evaluates 2 weeks of treatment, which is too short a time to see a response with alarm therapy [IIb]. In a sample of 24 children (12 per arm), Nawaz[99] finds a non-significant improvement with dry bed training in that 14 dry nights without relapse are achieved after a 6-month follow-up (RR=3.5; 95%CI 0.95-13.54) (it is striking that, the response rate with alarm therapy was only 16.6% in this study) [IIb]. In 24 children per arm, Butler[100] even observes poorer results with complex behavioral therapy versus alarm therapy in achieving 14 dry nights after 16 weeks of treatment with alarm therapy (RR=0.70; 95%CI 0.48-1.03) [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]**.

A study of 108 children aged 8-10 years (65 enuretics from a hospital enuresis clinic and 43 control children from a primary school), with an exam before and 6-10 months after receiving a CD containing information on enuresis, revealed that presenting information using multimedia format is effective in teaching the concepts of enuresis[101] [IV].

However, a multicenter clinical trial (that was neither blind nor randomized) including 270 children with enuresis failed to reveal differences in dryness rates

at 4 months of follow-up between three groups, those that received information (as the only intervention that was presumed to be curative) in the form of brochures, in multimedia format, or the control group[102] [IIIb].

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

10.2 How efficacious is the behavioral intervention with alarm therapy?

The alarm, a device that activates when it detects moisture, is one treatment for enuresis that is available in Primary Care.

Early alarm systems for enuresis were placed on the mattress where the child slept in the form of a net or mat and contained an electrical circuit that was sensitive to moisture. These were replaced in the 1980s by new miniature, portable systems that are more convenient to use, with a small sensor located in the child's undergarment or pyjamas that picked up the slightest degree moisture and triggered the system, usually with a sound, although there were also alarms that vibrated or emitted light. The alarm is set off after the first drops of urine, at which time the child should wake up, disconnect the system, go to the toilet, change his/her clothing if it is wet, and reconnect the system before going back to sleep. The system requires cooperation on the part of the family, particularly at the beginning, as well as from the child.

In Spain, there are a number of alarm models for enuresis on the market. They can either be bought on the Internet or in pharmacies and surgical aids shops or from companies that distribute medical supplies.

The success of the alarm mechanism is believed to lie in helping the child wake up in response to the sensation of a full bladder. This theory has not been proven and it does not account for one of the effects observed: an increase in nocturnal bladder capacity. When comparing voided volumes before and after treatment, an increase in bladder capacity was observed in the children treated, so many of those who needed to urinate at least once per night stayed dry without having to get up to go to the toilet after effective treatment with alarm[103] [IV].

Following the selection criteria previously described, 13 randomized controlled trials were identified (12 in Cochrane and another more recent one[104]). We will now analyze the available treatment options with the alarm approach:

A. Alarm/No intervention

In PMNE, alarm therapy is more efficacious than no treatment [IIb].

From the Cochrane Review and despite the heterogeneous nature of the studies, we can infer that for NE in general, alarm therapy is more efficacious than non-intervention. Even after treatment has been completed, the relapse rate is lower with alarm therapy, approximately 50% versus 99% in the control group[105].

Only one of these studies[106] fulfilled the criteria for PMNE. In this study, after randomizing to initiating alarm therapy or remaining on a waiting list, the response of 24 children aged 6-12 years who wet the bed more than 3 nights/week was evaluated. Fourteen weeks after starting the study, the number of wet nights was lower in children who had been undergoing alarm treatment (8.5% versus 60.83%). The relative risk of achieving cure (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]**.

B. Alarm/Other behavioral interventions

- Simple behavioral interventions

There is no evidence from clinical trials comparing outcomes of simple behavioral therapy with alarm therapy in children that only present PMNE.

- Complex behavioral interventions

Sufficient evidence is not available from quality, head-to-head clinical trials of alarm therapy and complex behavioral therapy in children with PMNE.

Only one clinical trial compares the results of alarm therapy with one of the complex behavioral intervention (dry bed training) in children with PMNE[98] [IIb]. The authors find that the percentage of dry nights is greater with the behavioral therapy than with alarm intervention, although these results should be interpreted cautiously: the treatment period is very short; a mere 2 weeks is insufficient to evaluate response to alarm therapy; there is no follow-up of the children, and very young children are included (3-14 years of age, of which some 40% are under the age of 6). With these data and a single study, we cannot draw any conclusions.

C. Alarm/Alarm associated with other behavioral interventions

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

Two randomized clinical trials have been selected that compare the alarm approach alone with the association of alarm therapy and *dry bed training*[100] [IIb] or *bladder retention training by toiletting schedule*[94] [IIb]. In both, the children had 4-6 wet nights/week; the sample size was very small; patients were followed up for 12-16 weeks, and 14 consecutive dry nights were considered a success. Neither of the two behavioral therapies evaluated demonstrated any benefit over alarm therapy alone (RR = 0.40; 95% CI 0.15-1.40 and RR = 0.56; 95% CI 0.16-1.99, respectively).

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

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

The Cochrane Review also examines *reinforcement* behavioral intervention, which consists of maintaining alarm therapy and administering an 'overload' of fluids before going to bed, once the child has managed to stay dry for least 14 consecutive days. In 2 clinical trials, that do not exclude children with daytime losses of urine, the authors conclude that relapses during follow-up of up to 3 years were lower if reinforcement was applied (25% versus 49%, RR = 1.92; 95% CI 1.27-2.92)[105] [Ia].

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]**.

Other behavioral techniques such as *penalization* in association with alarm therapy have not been evaluated in children with PMNE alone, albeit generally speaking, not only are they not beneficial, but are even counterproducti-

ve, increasing relapse rates after completing treatment[105].

D. What is the best alarm?

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

Only two studies by the same author meet our selection criteria. They compare different types of alarms (light, intermittent sounds, or different volumes of sound) over 6-7 weeks in children who had 3 to 7 wet nights/week. They failed to detect any differences between the different types of alarm (RR = 0.5; 95% CI 0.05-4.67)[107] and (RR = 0.5; 95% CI 0.17-1.46)[108].

In the Cochrane Review, which includes all types of NE, not enough evidence has been found to enable us to draw conclusions as to what the best type of alarm is[105].

E. Tolerability

Today's portable alarms are safe and well-tolerated **[Ia]**.

The only adverse effects of the alarm described[105][Ia] are:

- Alarm failure: moisture fails to trigger the alarm, either because it is not working properly or because of low battery.
- False alarms resulting from moisture from sweat, menstruation…
- It fails to awaken the child.
- It wakes up other members of the family.
- The child is frightened by the alarm.

The inability to wake up when the sound alarm goes off is a factor to be considered once treatment has started. In Butler's series of 66 children aged 6-16 years[109], the inability of the child to wake up to the sound of the alarm was a major factor in alarm treatment failure [IV].

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]**.

10.3 How efficacious is drug treatment?

Traditionally, tricyclic antidepressants and desmopressin are the drugs used to treat enuresis.

Even though tricyclic antidepressants are efficacious and have been the mainstay of medical treatment for years, their high toxicity (17.3% adverse

effects versus 5.3% for desmopressin)[110] [Ia] and even the risk of death due to accidental overdose, has precluded them from being recommended as the treatment of choice at present. Therefore, these guidelines only evaluate medical treatment with desmopressin.

Desmopressin

Vasopressin, also called arginine vasopressin (AVP) or antidiuretic hormone, is a short polypeptide (9-amino acid chain) produced by the hypothalamus and released by the pituitary gland. Its physiological role is to act as an osmotic regulator that increases the reabsorption of water thanks to its peripheral renal action. It is also a potent vasopressor by means of two mechanisms, the previously mentioned one that increases blood volume and a powerful, independent vasoconstrictor effect on the vascular tree, which gives it its name. It also acts on the smooth visceral muscles[111].

Physiologically speaking, vasopressin is released in response to stress, hypovolemia, or hypotension and has a very short half-life of 5-10 minutes. Some pathological situations may raise vasopressin levels while others lower them.

Desmopressin (DDAVP) is a polypeptide analogue of vasopressin created by the deamination of the cysteine residue in position 1 and replacement of L-arginine in the position 8 by D-arginine. These modifications endow the desmopressin molecule with a number of advantageous properties: it lacks any vasopressor effect, has higher antidiuretic effect, provides greater resistance to protease action, and has a half-life of 1.5-3.5 hours, which translated into the possibility of using an intranasal delivery system for the treatment for nocturnal enuresis at the end of the 1970s.

Desmopressin also triggers the release blood coagulation factors, such as factor VIII and the von Willebrand protein; hence, it is used at high doses in situations of risk in hemophiliacs[112].

Intranasal desmopressin crosses the blood-brain barrier and has also proven effects on the central nervous system. One of such effects is improved memory acquisition or short-term memory[113] [IIb]. A decrease in the ability to awaken has also been observed[114] [IIb].

Its partial resistance to intestinal proteases permits oral administration, although when given orally, its absorption rate is 10-20 times lower (bioavailability of 0.1-0.2%) than when administered intranasally (bioavailability of 3-5%); consequently, oral preparations are considered equally effective as intranasal when used at 10-20 times higher doses.

With oral administration, it does not cross the blood-brain barrier.

Factors affecting absorption differ from one route of administration to another. *Nasally*, acute rhinitis diminishes absorption. This effect disappears once acute symptoms have disappeared (this has been studied in pollen-allergy rhinitis outbreaks)[115]. No effects on absorption have been observed in less acute situations, such as allergy to dust mites[116].

Orally, no differences in absorption have been detected between administration immediately after dinner or 1.5 hours later. Under normal conditions, after dinner, absorption is slower than after fasting all night (peak concentration goes from 1.5 h following administration to 1 h) and less of the molecule is absorbed (maximum levels fall to approximately 50%), albeit these findings are not clinically relevant given that the antidiuretic effect in well-hydrated, healthy volunteers is similar with respect to time (onset at 30 minutes) and intensity, and is sustained over the 3 hours studied[117]. Agents that delay intestinal motility, such as loperamide, increase absorption 3-fold and prolong its effect beyond 8 hours[118]. It is thought that this effect might also occur in non-pharmacologically induced constipation. Protease enzyme inhibitors, such as aprotinin (uncommon in clinical practice), increase absorption by a factor of 5[119]. Agents that stimulate intestinal motility (erythromycin) have no effect on intestinal absorption[118].

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]**.

How efficacious is desmopressin?

A systematic review of the Cochrane Library up to March 2002 located 41 randomized or quasi-randomized studies that included desmopressin in at least one arm. Of these, 36 contributed sufficient data to make them evaluable. Of the 20 that make it possible to compare desmopressin to placebo, we have selected only 10 that expressly excluded organic causes or that claimed to examine only monosymptomatic enuresis (no daytime losses), and only 5 provided data regarding cure defined as complete dryness or initial response (100% dry nights) or at least complete response (> 90% fewer wet nights).

Pooled analyzes of the data were conducted when outcome measures were complete dryness or complete response and were comparable.

A. Desmopressin versus placebo

The pooled analysis of two studies[111,120] revealed that desmopressin is an efficacious treatment (compared to placebo) for PMNE, given that it decreases the number of wet nights by 1.58 nights/week (95%CI 1.09-2.08) [IIb].

From the standpoint of treatment, results depend on the objectives. If a partial response is sought (reduction of 50%; for example, going from 6-7 wet nights/week to < 3 wet nights/week), the probability of success is 2.44 times greater than with placebo (RR = 2.44; 95% CI 1.47-4.12)[121]. When the objective is complete dryness, the pooled analysis of two studies[111, 122] 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]**.

Skoog et al performed a double-blind, randomized, placebo-controlled, multicenter clinical trial that included three treatment arms of oral desmopressin (placebo, 0.2, 0.4 and 0.6 mg) in 148 subjects with PMNE with ages of 7 to 17 years. At Weeks 4 and 6, the 0.4-mg dose achieved 12% (4/34) complete dryness; versus zero percent in the placebo group (0/36) (RR = 1.14; 95% CI 1.0-1.3) (NNT = 9; 95% CI 4-500)[122] [IIb]. It is very important to properly define the aim treatment pursues, since the same study yielded better figures when only a partial response was established as the objective (lowering the number of wet nights to ≤ 2/14 days): 32% (11/33) versus 3% (1/33) in the placebo group (RR = 11.0; 95% CI 1.5-80.4 and NNT = 3; 95% CI 2-8)[122].

Although this analysis does not indicate that desmopressin is particularly effective in achieving complete dryness, in clinical practice, this may not be entirely true because these studies select heavy wetters for methodological purposes in order to evaluate percentages of response in a short period of time. However in doing so, poor prognostic factors for desmopressin are selected, as we shall see later, such that outcomes in milder cases of enuresis would probably be better.

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

B. Dosage

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.

The most relevant study that compares the efficacy of different intranasal doses also included non-monosymptomatic enuresis. It is a double-blind, randomized, crossover study of 22 children with protracted enuresis that was refractory to other treatments. There were no differences in the number of dry nights/week over the 4-week treatment period between the 20-µg and 40-µg arms[123] [IIb]. There were not enough cases to confirm non-inferiority of one dose against the other.

The pooled analysis of two studies[111,122] that analyze the response to oral desmopressin in heavy wetters with PMNE demonstrated that its efficacy in lowering the number of wet nights is dose-dependent. The mean difference in the reduction of wet nights was 0.5 nights/week greater with 0.4 mg than with 0.2 mg (95% CI 0.06-0.94); when comparing doses of 0.2 and 0.6 mg, the difference was 0.72 nights greater (95% CI 0.30-1.14) [Ib].

However, when the goal was to attain 14 dry nights, there were no differences between the different doses, although there were not enough cases to confirm non-inferiority of one dose versus another[111,122] [Ib].

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]**.

C. Intranasal/oral route

Despite the fact that comparative studies of the oral route versus the intranasal mode of delivery have not been po-

wered 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]**.

There is only one study in children with PMNE (n = 30) that fails to detect differences in efficacy between 0.2 mg of oral desmopressin and 20 µg intranasal desmopressin[119] [IIb]. Another randomized study (of adults and adolescents) (n = 66) comparing 20 µg intranasal with 0.2 or 0.4 mg oral desmopressin also failed to find clinical differences between the different doses and routes of administration[124] [IIb]. However, the number of cases in both studies was insufficient to confirm the non-inferiority of oral administration.

D. Onset of effect

In a comparative study with alarm treatment, the effect of desmopressin was already apparent in the first week of treatment[125] **[Ib]**; although the maximum effect of fewer wet nights was seen at week 4 **[Ib]** of initiating treatment at doses of 0.2 and 0.4 mg, and at week 6 with a dose of 0.6 mg[122] [Ib].

E. Tolerability

Few secondary effects have been described (4.6%) in 826 children treated with oral and intranasal desmopressin in 13 clinical trials: anorexia (1 case), headache (10), rash/dermatitis (2), visual (1) and taste disturbances (2), vomiting (1), nasal discomfort (19), and epistaxis (4), most of which were related to intranasal administration[70]. In double-blind studies versus placebo, there were no differences in the incidence of adverse events between both groups or were unrelated to treatment[70].

Long term, there are also few descriptions of adverse events with oral administration. In a cohort study of 25 children with 5-7 years follow-up, no growth disturbances were detected and only one patient discontinued treatment at 6 years due to nausea[126]. A Canadian cohort of 256 children with a 1-year follow-up yielded an estimated 0.8% rate of adverse events that were possibly related to desmopressin: 1 abdominal pain + 1 abdominal pain and headache. There were no alterations of blood pressure, water or electrolyte balance, or heart rate, nor were creatinine or hepatic enzymes affected[127].

Side effects of desmopressin are very uncommon and almost never require treatment withdrawal. The adverse effect that can and must be prevented is water intoxication. Since 1974, twenty-eight cases have been reported, all with intranasal administration[128,129]

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[70,129-132] **[D]**.

There have also been cases of overdosing, without serious consequences, either accidentally or when the child thought that a higher dose would have a greater effect[125].

Desmopressin is a safe drug, both in the short and long term. Adverse effects are uncommon and less when administered orally [Ia].

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]**.

F. Treatment duration

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]**.

In a study of 55 children with enuresis, Evans[133] found no difference in rates of complete dryness at one month (28 children) versus 3 months (27 children) of treatment (RR = 0.62; 95% CI 0.16-2.35). Nor were differences seen in the cure rate; there was 1 in each group (RR = 1.04; 95% CI 0.07-15.76) during follow-up of these patients [IIb].

The duration of long term treatment is limited by the appearance of toxicity or loss of efficacy. Neither situation occurred in the cohort studies with a 6-month follow-up (intranasal)[134] or 1 year[127,135] and 5-7 years[126] (oral administration).

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]**.

G. Relapses after treatment completion

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

There are no studies that evaluate relapses when treatment with desmopressin is discontinued in children with

PMNE; hence, we must quote results from the Cochrane review that includes children with non-monosymptomatic enuresis. No differences were observed between active treatment and placebo groups during follow-up after completion of treatment with desmopressin[70].

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

• Tapered dose reduction withdrawal

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

Tapered dose reduction withdrawal was popularized by a study of cases series published in 1998 in which a 71% cure rate was attained in an average treatment period of 28 weeks and at a maximum of 2 years[136] [IV]. These results, however, have not been replicated since then.

• Structured withdrawal (gradual, intermittent withdrawal at full doses)

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]**.

In 2001 Butler et al evaluated a group of 51 children with PMNE, either complete responders to desmopressin (37 children) or tricyclic antidepressants (14 children) who had relapsed after more than 4 months of treatment with two prior attempts at discontinuing medication using decreasing doses. They received the same treatment that had failed, following a structured withdrawal program, at full doses but administered every 2 weeks with more days without medication (table I). The children had previously decided whether to take nothing (24 cases) or to use alarm therapy (27 cases) on the days they didn't take medication. This system involved the children so they could analyze the key factors in staying dry on those days, and thus, they internalized the attribution of success from an external source (the drug) to an internal one (the change in self).

This regime improved long-term outcomes, given that from no response in 2 prior treatment discontinuations, relapse-free cure was achieved at 6 months in more than half of the patients (27/51 52.9%) with the same drug, regardless of whether they had used alarm therapy or not[137] [IIb].

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

H. Association with other treatments

• Desmopressin associated with alarm

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

A double-blind, randomized, clinical trial with 93 heavy wetters (≥ 6 nights/week) with PMNE aged 6-14 years compared the effect of alarm therapy over 9 weeks associated with placebo or desmopressin during the first 6 weeks. During the first 3 weeks, a better response was seen in the group that associated desmopressin (p = 0.014). Response was similar during the last 3 weeks in which only alarm therapy was used in both groups. Likewise, 6 months after completing treatment, there were still no intergroup differences (36% cure rate) (RR = 1.07; 95% CI 0.68-1.70)[138] [Ib].

Another clinical trial was excluded due to the short treatment period of only two weeks, which we consider insufficient for alarm treatment[139].

A Spanish study that enrolled 59 children with ages from 7-14 years who wet the bed > 1 night/week also failed to detect any advantage in the association of desmopressin and alarm (RR = 1.66; 95% CI 0.79-3.47)[140] [IIb].

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 a night, the use of desmopressin might be recommended with the aim of decreasing the number of nocturnal micturitions to just one, to make alarm therapy more tolerable **[D]**.

• Desmopressin associated with anticholinergics

In urological practice, drug associations are commonly used such as antidepressants with anticholinergics, or desmopressin with anticholinergics or antidepressants, particularly when desmopressin or anticholinergics fail in monotherapy. Antidepressants aside (due

to toxicity) and given the appearance of new, safer, and more specific bladder anticholinergics, we have considered it essential that the evidence on the association of desmopressin with anticholinergics in PMNE be reviewed.

Anticholinergics have been the mainstay of therapy in non-monosymptomatic enuresis with the aim of controlling detrusor overactivity.

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

Cendron et al[141] selected a series of 28 cases of persistent enuresis (9-18 years of age) in which medical therapy (desmopressin, anticholinergics, or imipramine) had failed. They associated a long-acting anticholinergic, hyoscyamine (0.375 mg) with desmopressin at bedtime. The results showed 57% (16 of 28) complete dryness at 6 months of treatment. This response rate was higher than expected for desmopressin alone in non-refractory patients [IV].

Neveus et al[84] selected a series of 28 heavy wetters (≥6 nights/week) with PMNE who had not responded in a previous clinical trial or had relapsed after treatment with desmopressin. The participants received an open-label combination of 0.4 mg oral desmopressin and 5 mg of oxybutynin at bedtime. There were 13 responses of complete dryness (46%); once again, higher than expected for desmopressin alone in patients who had not been previously selected.

Rodríguez do Forno et al[140] evaluated 25 children with PMNE aged 6-7 years in Primary Care in whom a 6-month course of treatment with desmopressin was initiated. Eight (32%) responses of complete dryness were obtained. In the non-responders, oxybutynin was associated and 53% (9 of 17) achieved remission (RR of cure versus desmopressin alone = 1.65; 95% CI 0.80-3.42)[140] [IV].

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

I. Strategy with alarm therapy following desmopressin failure

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

Only one clinical trial[104] has been selected with a high level of evidence [Ib] that evaluates the combination of both

treatments in children recruited from Primary Care.

The study enrolled 358 children aged 6-16 years (mean age of 8) who wet the bed ⩾ 2 nights/week. Children with a medical condition were not included, although some children with daytime incontinence were.

After a 4-week trial treatment period with desmopressin (20-40 mg), those children who responded were excluded (> 50% decrease in the number of wet nights).

The 207 children who did not respond (19 of them with daytime losses) and who wet the bed an average of 6 nights/week were randomized to 2 arms: 101 children were treated with alarm + desmopressin (the dose was not stated) and 106 children with alarm + placebo.

For the 8 weeks of treatment there were fewer wet nights in the group that received desmopressin, although during follow-up (8 weeks after completing treatment), the remission rate (28 consecutive dry nights) was seen to be similar in both groups (approximately 50%) as was the number of relapses (wetting more than 2 nights in 2 weeks after remission) between both treatment arms. On separating the group of children with daytime symptoms, the results remained unchanged.

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

10.4. Advantages/disadvantages of different treatments

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]**.

Two clinical studies have been selected that compare alarm and intranasal desmopressin in heavy bedwetters (⩾ 3 nights/week). Only one assesses relapse rates upon treatment completion. In both studies, success criteria are less strict than those accepted in these guidelines (only 12 dry nights out of 14). A third trial was excluded due to the high dropout rate (44%) and the switch from the treatment initially assigned by randomization to another treatment in many patients[142].

In the very short term (1 week), response to desmopressin was much better than to alarm therapy. However, the ef-

fects evened out at three weeks[125]. In the pooled analysis of both studies[59,125] no differences were found between alarm and desmopressin at 3-6 months of maintained treatment (RR = 0,76; 95% CI 0.53-1.1) [Ib]. In contrast, 3 months after completing treatment, there were almost one quarter as many relapses in the group with alarm treatment (RR of failure or relapse = 0.27; 95% CI 0.11-0.69)[125] [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]**.

The advantages and disadvantages are summarized in table III.

10.5. Prognostic factors of treatment response

When deciding on treatment, it is important to know if there are prognostic factors of good or poor response to available therapies, as they can be decisive in treatment success. There are extremely few studies that evaluate these pre-treatment factors and are at times, poor quality studies. Whenever possible, prognostic factors for alarm therapy (table IV) or desmopressin (table V) have been evaluated separately. There are no studies of prognostic factors for behavioral interventions other than alarm therapy.

A. Sex

There is evidence that gender has no impact on the success of different treatments **[Ib]**, although it is known that the proportion of wet nights in enuretic girls tends to be higher than in boys[143].

Alarm treatment

Several studies have shown that gender has no influence in treatment response to alarm therapy[109,143-145] [Ib].

Desmopressin

All the studies reviewed have shown that children of both sexes respond equally to desmopressin treatment[146-148] [Ib].

Gender is not a prognostic factor to be taken into account when initiating therapy with alarm or desmopressin **[A]**.

B. Age

Alarm treatment

Age is not a factor that affects response to alarm therapy **[Ib]**.

Studies of children with PMNE that have evaluated age have demonstrated that it has no effect on treatment success or failure with alarm therapy[109,143-145] **[Ib]**.

Desmopressin

There are no studies with suitable clinical response criteria that evaluate the influence of the age as a prognostic factor response to desmopressin.

Only 2 clinical trials of sufficient quality have been found[146,147] [Ib] that deal with the factor of age. However, none of them include multifactorial analysis that includes confounding factors such as the baseline frequency of wet nights, given that it is known that the frequency of wet nights tends to decline after the age of 10[143] [IV]. Another consideration regarding these studies is the response criterion. Both Rushton[147] and Kruse[146] define a "responder" as a child with a > 50% decrease in wet nights, which does not comprise a valid clinical response criterion. Although they observe that older children respond better, these previous considerations make the findings useless in decision-making; we therefore cannot make recommendations on the basis of age.

Age is not considered a decision criterion in treatment selection **[A]**.

C. Inheritance in enuresis

Alarm

There are no studies that evaluate the influence of inheritance on alarm therapy.

Desmopressin

A family history of enuresis has no impact on the success or failure of treatment with desmopressin**[Ib]**.

In a study of 399 children with PMNE in Primary Care, Kruse evaluated a 4-week course of treatment (preceded by 2 weeks dose titration) with intranasal desmopressin. In the univariate analysis, no association was found between "inheritance in enuresis" and a worse prognosis of response to desmopressin (with a partial response criterion of > 50% of dry nights)[146] [Ib].

Rushton conducted a double-blind study with intranasal desmopressin versus placebo in 96 children and also

failed to find differences in family history of enuresis between responders and non-responders (with a partial response criterion of > 50% dry nights)[147] [Ib].

Family history of enuresis does not intervene in the choice of treatment **[B]**.

D. Prior treatments

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]**.

Alarm

Among other factors, Devlin et al[145] investigated the influence of previous treatments on response to a new treatment with alarm in 96 patients. With the objective of achieving partial response, they concluded that the existence of prior treatments does not modify the success or failure rate of alarm therapy [Ib].

Desmopressin

Only Kruse et al[146] assessed this factor in a study of 399 children with PMNE in Primary Care. They carried out a 4-week course of treatment (preceded by 2 weeks of dose titration) with intranasal desmopressin and with a criterion of full response (90% fewer wet nights). The univariate analysis found no association between prior treatment failure (alarm, desmopressin, combination of both, or no treatment) and poor response to desmopressin [Ib].

E. Number of wet nights

The severity of enuresis (usually assessed in terms of number of wet nights per week) is one of the factors that influence treatment response. Unfortunately, the studies located that dealt with prognosis only evaluate children who wet the bed more than three nights per week, and there is only one study with desmopressin that evaluates mild or moderate severity.

Alarm

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

A Danish study[143] concluded that the greater the number of wet nights prior to treatment initiation, the greater the

probability of staying dry one year after completing alarm therapy, i.e. children who wet the bed every night had a better prognosis [IV]. One year after completing treatment the authors evaluated the situation of children with nocturnal enuresis over 5 years of age who had been successfully treated with alarm therapy. They all wet the bed ⩾3 nights/week prior to treatment and success was considered ⩾21 consecutive days of dry nights in 6 weeks of treatment.

A meta-analysis of 35 cohort studies[149] since alarm therapy started in 1939 showed that, at all times, the more wet nights per week, the greater the success of alarm treatment. The number of consecutive dry nights necessary to consider the treatment a success ranged from 7 to 56 nights, depending on the studies and eras. Success rates were higher in older publications which probably has to do with the stringency and follow-up of the published studies (failures, losses to follow-up, confounding factors) and a stricter definition of success (more consecutive dry nights) in recent years [IIa].

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.

Desmopressin

In a group of 132 children with monosymptomatic nocturnal enuresis, Hamano et al treated 54 heavy wetters (6-7 wet nights/week) with desmopressin and did not find a difference in response in those who wet the bed 6 or 7 nights/week[96] [Ib]. However, in a study with 66 children with PMNE aged 8 to 14 years who wet the bed ⩾ 4 nights/week, Butler et al[148] found a better response at week 4 of treatment with desmopressin (oral or intranasal) in those who wet the bed fewer nights/week [Ib]. Despite the high level of evidence in this study, it is a pity that it does not provide numerical data that would aid in making decisions on the basis of the evaluation of these pre-treatment factors.

Using rather lenient response criteria, Rushton et al[147] found similar results.

They evaluated 96 children with PMNE and aged 8-14 years who wet the bed at least 6 nights a week. They analyzed partial response (≥ 50% fewer wet nights) at 4 weeks of treatment with 20-40 µg of intranasal desmopressin. They obtained data on 95 children and, by means of univariate analysis, observed that the children who wet the bed less responded better than the others [Ib]. Therefore, in contrast with alarm therapy, having fewer wet nights prior to initiating treatment is a positive predictor for treatment outcome with desmopressin **[Ib]**.

One thing to be considered is that most of the studies on treatment have a selection bias for the evaluation of the frequency of wet nights, given that they always select heavy wetters. There is only one study that evaluates children who wet infrequently (1-2 nights/week), in 25 young children (6-7 years of age) who were given 20-40 µg of intranasal desmopressin[140]. Once it was effective, it was maintained for 6 months and then withdrawn in a tapered dose reduction mode. Of all the study participants, 6 wet very little and all were cured (dry after 1 year) and 2 of the 19 heavy wetters were cured and 1 relapsed when desmopressin was withdrawn (RR = 9.50; 95% CI 2.56-35.24). From this study we can deduce that 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]**.

F. Number of incidents per night

Alarm

There are no studies that evaluate this factor in alarm therapy.

Desmopressin

The number of wetting incidents per night does not influence treatment with desmopressin **[Ib]**.

The influence of the number of wetting incidents per night has only been studied within the context of desmopressin treatment and was considered to be a prognostic factor for this treatment. Kruse et al[146] observed that children who wet the bed only once a night responded better to treatment with desmopressin than those who wet more than once, although in the original study success was defined as 50% fewer wet nights, which is clinically irrelevant. On the basis of the data derived

from this study, if > 90% fewer wet nights is considered a response criterion, the fact that a child wets just once every night rather than more than once does not have any bearing on this treatment (RR = 0.65; 95% CI 0.34-1.25) [Ib].

G. Maximum daytime voided volume

Alarm

An MDVV < 45% of the predicted value for the child's age according to Koff's formula is a factor of poor prognosis for alarm therapy **[IV]**.

MDVV has also been mentioned as a prognostic factor for response to alarm therapy, although the data available to date are of poor quality. The best evidence found is Butler's series of 66 children with PMNE[109] who wet the bed at least 4 nights/week. In this study, 75% of the children in whom treatment had failed had a MDVV that was less than 50% of the MDVV predicted for their age (less than 45% using Koff's formula[89]) [IV].

Desmopressin

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]**.

Only 2 clinical trials evaluate MDVV as a prognostic factor of response to desmopressin.

Hamano et al[96] evaluated treatment response in 132 children with PMNE who wet the bed ⩾ 4 nights per week. One arm of 54 children was randomized; they received intranasal desmopressin for 12 weeks: starting at a dose of 5 µg/night and titrating up to 20 µg/night and attempting to maintain the patient at the minimum effective dose. The response criteria were fairly close to complete response (reduction ⩾ 87.5% wet nights). The MDVV was determined prior to treatment as the 5-day maximum urine volume. Treatment response rates with desmopressin differed depending on whether the MDVV was above or below 75% of the predicted level for the age, according to Koff's formula. The RR of failure when the MDVV was ≤ 75% was 3.54 times greater (RR = 3.54; 95% CI 1.81-6.90) than when it was > 75%) [Ib]. With the data of this study we can estimate that when the MDVV is > 75% of the theoretical figure, complete response will be attained in 76.5% of the patients (95% CI 52.7-90.5) versus 21.6% (95% CI 11.4-37.2) otherwise.

Another study[147] also evaluated response to desmopressin on the basis of MDVV. It included 96 children aged 8-14 with PMNE who wet the bed at least 6 nights/week. Despite the fact that the response criteria were only for partial response (clinically irrelevant), their results coincide with the previous study [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).

H. Maximum nighttime voided volume

There are no studies that analyze the importance of the maximum nighttime voided volume (first morning void). We believe these data would be of great interest because it reflects bladder behavior during sleep.

I. Family or child attitudes

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]**.

Alarm

Parental attitude regarding enuresis is an important element in the success of alarm therapy, and in this respect the study by Morgan and Young[150] is interesting. Using a 20-question survey of mothers during the initial visit to the doctor, the study evaluated the factors associated with the disapproval and annoyance generated by their children's bedwetting. They observed that dropout rates with alarm therapy were higher in disapproving mothers and that mothers from lower socioeconomic groups were less tolerant and more annoyed by their children's enuresis. In contrast, neither the child's age, gender, severity of enuresis, type of enuresis (primary or secondary) nor family history of enuresis was associated with disapproval or annoyance [IV].

Other studies have also demonstrated that high parental disapproval of their children's enuresis, as evaluated using

the Morgan and Young scale, predict a high probability of dropout from alarm therapy but not drug treatment[106,144] [Ib]. It has also been seen that both parental concern for the child's problem and the child's concern about his/her condition create an atmosphere of motivation and collaboration; hence, they constitute factors of good prognosis for starting alarm therapy[145][Ib]. Moreover, children perceived by their parents as less withdrawn and better adapted socially have a higher probability of achieving success with alarm treatment[106][Ib].

Desmopressin

Unlike what happens with alarm treatment, parental disapproval of enuresis does not influence treatment with desmopressin[106,144][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]**.

J. Neuropsychological/psychiatric problems

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

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[145] **[Ib]**.

ADHD is a diagnosis to be taken very much into account in enuretic children when undertaking treatment. There is an interesting case-control study that was recently published on this subject that compares drug therapy and alarm in enuretic children with ADHD. It is a 16-year, retrospective study that evaluated response to different treatments for enuresis one year after initiating them in children with enuresis and ADHD who were being treated for this disorder. One hundred and thirteen children with PMNE + ADHD were compared with 113 controls with PMNE, but without ADHD. The authors observed that the response rate to behavioral alarm therapy was significantly lower in children with ADHD than in the control group (RR = 0.3; 95% CI 0.17-0.51). Three weeks after starting alarm therapy, compliance in ADHD children was lower (RR = 0.55; 95% CI 0.30-0.99). On the other hand, when treatment with desmopressin was evaluated, the response was similar to the control group (RR = 1.05; 95% CI 0.73-1.53.)[151] [IIb].

Desmopressin

Our review of the repercussions of psychological/psychiatric factors on response to treatment with desmopressin only detected the afore-mentioned study by Crimmins et al[151]. It concluded that ADHD co-morbidity in children with enuresis is not a factor of poor prognosis for drug therapy when compared to controls (RR = 1.05; 95% CI 0.73-1.53)[151] [IIb] unlike what happened with the alarm treatment.

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

K. Rey-Osterrieth complex figure test

Alarm

There are no studies that evaluate this test as a prognostic factor for alarm therapy.

Desmopressin

The Rey-Osterrieth Complex Figure Test has been used by neurophysiologists and clinical psychologists to analyze different cognitive skills: organizational and planning skills, problem-solving strategies and memory, motor and perception functions. Changes in the ability to copy and recall this figure have been studied in relation to developmental changes in children.

Andronikof-Sanglade et al[152] observed that "boundary-type errors" in the figure were closely correlated to the growth hormone neurosecretory dysfunction syndrome (children who have adequate levels of this hormone but low nocturnal endogenous secretion). These "boundary-type errors" also comprised a finding in children of low stature and were not characteristics of normal developmental changes or related to intellectual coefficient.

Bosson et al[153] studied the prognostic value of this test in 34 children in Primary Care (nursing clinic) with the following inclusion criteria: age ⩾ 7 years, PMNE, average frequency of bedwetting of 4 wet nights/week and no learning problems.

The test was performed in two stages: first, the child was asked to copy the figure onto a blank piece of paper (no time limit). Once completed, both (the model and the child's reproduction) were removed from the child's sight for about 3 minutes. During the second stage, the child was asked to reproduce the figure by heart[153].

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

L. Hypercalciuria

Alarm

There are no studies that evaluate this test as a prognostic factor for alarm therapy.

Desmopressin

In addition to antidiuretic hormone deficiency, one of the causes of nocturnal polyuria described in monosymptomatic enuresis is nocturnal hypercalciuria, which is believed to be related to the same biochemical mechanisms as adiuretin, and which might be a factor of poor prognosis of response to desmopressin[154] **[IV]**.

In a series of 406 children with PMNE, Pace et al[155] compared 21 desmopressin refractory cases with 385 who had responded to this drug. The 21 cases presented nocturnal polyuria and nocturnal hypercalciuria, labeled as absorptive. Hypercalciuria treatment (diet poor in calcium and sodium) is considered an important factor of successful treatment for enuresis, although 12 of the 21 children also required desmopressin [IV].

In the discussion, the authors suggest that the urinary Ca/creatinine ratio should be studied in all patients with monosymptomatic enuresis and nocturnal polyuria. The low level of the evidence [IV] from this single study would only allow us to recommend it in treatment failures in a hospital setting, where the most refractory cases are most likely to arrive.

There is not sufficient evidence to recommend urinary Ca/creatinine ratio determinations in children with PMNE and nocturnal polyuria in Primary Care, although it could be examined in those children who have failed on desmopressin **[D]**.

M. Factors studied with no bearing on prognosis

Alarm

As with age and gender, the following also have no bearing on alarm therapy success/failure: place of residence (rural/urban), social class, parental employment status, adverse architectural elements at home, size of the family, and birth order[145] **[Ib]**.

Desmopressin

Demographic factors, parental concern, parental tolerance of enuresis (assessed by means of the Morgan and Young scale), parental self-esteem[148] [Ib], and urinary osmolarity[147] have no impact on treatment with desmopressin [Ib].

N. Other unquantifiable factors studied

In one study, other prognostic factors of poor response to desmopressin have been described that are difficult to interpret: low birth weight and parents who try to get the child to drink more[148] [Ib].