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Long-term desmopressin response in primary nocturnal enuresis: open-label, multinational study

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SUMMARY

Background: Primary nocturnal enuresis (PNE) is a distressing condition, particularly in severe cases (≥ 3 wet nights/week). A prevalent pathophysiological mechanism, especially in monosymptomatic PNE (PMNE), is commonly believed to be an insufficient increase in night-time release of antidiuretic hormone. Desmopressin, a synthetic analogue of antidiuretic hormone, has been shown to reduce the number of wet nights experienced by PMNE patients in several controlled trials. **Aim:**This study was performed to evaluate desmopressin treatment in the real-life clinical setting and was a large-scale, 6-month investigation of efficacy and safety in patients with severe PNE. Predictive factors for desmopressin response were also evaluated. A total of 744 children aged 5 years and above from four countries were involved in the study. **Results:**At baseline, patients had a median of 6 wet nights/week; at 6 months, 41% of patients had experienced ≥ 50% reduction in the mean number of wet nights. Long-term desmopressin treatment was consistently well-tolerated across all ages, with 5% of patients experiencing any treatment-related adverse events. The strength of treatment response was associated with nocturnal diuresis ($p < 0.0001$) and age ($p = 0.0167$) in logistic regression analyses. Compliance and dosage were also associated with response and more patients experienced ≥ 50% reduction in wet nights after 6 months' treatment than earlier in the study, suggesting the value of persistent treatment. **Conclusion:**This study shows that long-term desmopressin treatment in the clinical setting is effective and well-tolerated in PNE patients of 5 years and upwards. Early improvements in bedwetting of any appreciable magnitude may be rewarding, may facilitate compliance and enable good long-term response.

What's known
Previous clinical trials have demonstrated the efficacy of desmopressin in PNE treatment.

What's new
This study provides an evaluation of desmopressin as a first-line treatment in a broad population of unselected, treatment-naive patients, representative of those seen in the real-life clinical setting.

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Disclosures
Bjarke Mirner Klein and Jens Peter Norgaard are employees of Ferring Pharmaceuticals and the DRIP study was sponsored by a research grant from Ferring Pharmaceuticals Ltd. Jonathan Evans and Henri Lottmann have received payment from Ferring Pharmaceuticals for advisory work and lecturing and have received sponsorship to present research at educational meetings. Paul Eggert and Lola Baydala have no conflict of interest to declare.

Clinical Trials.gov
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Introduction

Enuresis or bedwetting is the leakage of urine while sleeping in children aged 5 years or older (1). The word 'nocturnal' is usually added to enuresis for extra clarity and primary nocturnal enuresis (PNE) refers to children who have never been dry at night for an uninterrupted period of at least 6 months (1). Bedwetting is a distressing problem that affects between 6 and 10% of children aged 7 years (2–5). Those affected are vulnerable to a number of social and emotional issues arising from the condition and their associated embarrassment; these include low self-esteem, anxiety and withdrawal from socialisation (6,7). Bedwetting was ranked as the third most traumatic event, after parental divorce and parental fighting, by a sample of 8–16 year olds (8). Parents of affected children also experience a considerable burden relating to PNE in terms of the emotional demands of caring for a child who may be upset about their bedwetting, the difficulties associated with spending nights away from home, as well as the cost and time involved in laundering bedclothes (9). The annual spontaneous resolution rate of bedwetting is approximately 10–15% (10), but the condition can persist into adolescence and prevalence in young adults is estimated to be up to 3% (11–13).

Bedwetting in children has a multifactorial aetiology; however, it is widely acknowledged today that the main cause for primary monosymptomatic nocturnal enuresis (PMNE) is a mismatch between nocturnal bladder capacity and nocturnal urine production (12). This has been shown to have relevance for evaluating patients with PMNE and also for implementing the right treatment. In cases of nocturnal polyuria, which in some patients has

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been shown to be caused by insufficient arginine vasopressin (AVP) release at night (14,15), antidiuretic treatment with desmopressin has been shown to be effective (16,17). Desmopressin is endorsed by the International Consultation on Incontinence (ICI) as a first-line treatment for bedwetting of polyuric origin (level 1, grade A) (12) and constitutes a well-tolerated, rapid-acting treatment option for children with very few side effects (16,18–20). In patients with low bladder capacity, alarm treatment has become standard and is also endorsed by the ICI. A combination of these two treatments has also been proven as an effective evidence-based treatment (12).

Recently, a new theory has been proposed that some of the therapeutic effect of desmopressin is exerted through an effect on the central nervous system, with a signal cascade on relevant reflex mechanisms (21). It is therefore clear that there is a diverse pathophysiological mechanism behind PNE and consequently, there is also a diverse therapeutic spectrum in which desmopressin plays a central role.

Although numerous clinical trials have demonstrated the efficacy of desmopressin in PNE treatment, this study addresses the need for an evaluation of the efficacy of desmopressin as a first-line treatment in a broad population of treatment-naïve patients, who are representative of those children seen in the real-life clinical setting. This study is the largest investigation of desmopressin as a therapeutic intervention in PNE over an extended 6-month period in children aged 5 years and above from four different countries.

This study also provides a comprehensive analysis of factors that may predict the success of desmopressin treatment. Whilst factors that are predictive of response to treatment have been explored in previous studies, these have often involved only a small number of patients (22–24). Results have variably implicated factors such as endogenous AVP levels, history of breast feeding, family history of enuresis, age of child and bladder capacity as predictors of response to desmopressin treatment (24–27). Given the large sample size in this study, analyses were expected to generate replicable findings regarding predictive factors, which might aid the physician's selection of the most appropriate treatment for individual PNE patients. The long-term nature of this study meant that the inclusion of a placebo arm was inappropriate. The study explores efficacy in a natural, non-comparative setting and investigates whether factors which can be assessed at baseline are predictive of response to desmopressin treatment.

Methods

This was a 6-month, open-label, phase IV study performed in 86 centres in four countries (Canada, France, Germany and the UK) in accordance with the Declaration of Helsinki (28) and in compliance with the approved protocol, good clinical practice and applicable regulatory requirements. Freely-written consent was obtained from all patients or informed consent was obtained from the parent or guardian, where appropriate. Four countries were included in the study because of the phase IV nature of the trial. For reasons of differences in local labelling for desmopressin, however, small variations in the study protocol were required, as described below.

Patients

Patients with previously untreated PNE, or treatment-naïve patients (children who had been treated with desmopressin – or other medications for nocturnal enuresis – or enuresis alarms more than 1 year ago and/or with a treatment duration of < 4 weeks), were enrolled into the study. Inclusion criteria included severe PNE, defined as ≥ 6 wet nights during the 2-week screening period and 5–17 years of age (6–17 years in France). To select children with PMNE, patients were excluded if they had diurnal symptoms such as urgency, frequency and/or day wetting, suffered from encopresis, diagnosed renal or central diabetes insipidus with AVP deficiency or a known urinary tract infection within the past month. Also excluded were patients known to have syndrome of inappropriate antidiuretic hormone secretion and/or cardiac failure or with clinically significant diseases or medication that may have been considered to interfere with the evaluation of the study or with desmopressin activity.

Study design

The study design is summarised in Figure 1. Patients underwent an initial 2-week screening period, during which they received no medication. During the subsequent 2-week run-in period, all patients received 0.2 mg desmopressin [in Canada, run-in could be extended to 4 weeks (second run-in period), titrating to 0.4 mg if ≥ 2 wet nights were experienced during the first 2 weeks of run-in]. Patients then entered the first of up to two 3-month treatment periods (6 weeks in Germany). In the UK, Germany and France, children who experienced ≤ 1 wet night over 2 weeks during run-in were administered 0.2 mg desmopressin in both treatment periods, and those experiencing > 1 wet night were administered 0.4 mg desmopressin in both treatment periods. In Canada, patients who experienced ≤ 1 wet night during the

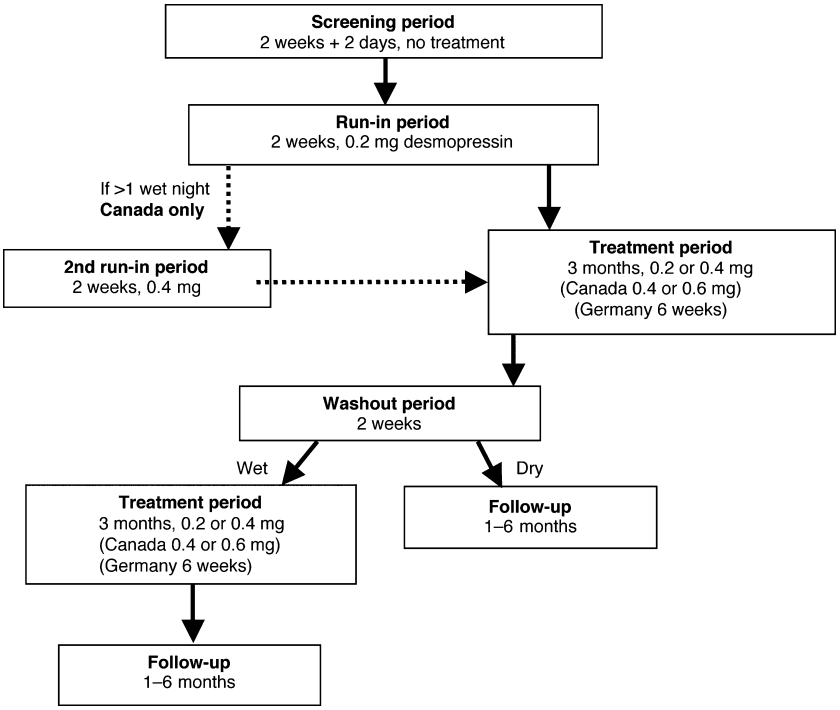

Figure 1 Study design

first run-in period were administered 0.2 mg desmopressin for both treatment periods. Those who experienced > 1 wet night during first run-in continued into the second run-in on 0.4 mg. If these patients experienced ≤ 1 wet night in the second run-in period, they were administered 0.4 mg in both treatment periods. If they experienced > 1 wet night during second run-in, they received 0.6 mg desmopressin in both treatment periods.

The first treatment period was followed by a 2-week washout period with no study medication. Patients, who were dry after the washout period, entered a 6-month follow-up period, during which desmopressin was no longer administered. Patients who were wet after the washout period continued to a second 3-month treatment period (6 weeks in Germany), followed by a 6-month follow-up period.

Tablets were taken 1 h before bedtime. The patients were advised to drink only to satisfy thirst 1 h before and 8 h after taking study medication. Study medication was not permitted if the patient had been drinking an excessive amount of fluid, or in cases of high fever or illness requiring high fluid intake.

Diaries were completed by the child (parents assisted younger children). Patients/parents recorded whether the preceding night was wet or dry, or whether the child voided at the toilet or not. The 2-week diary was completed during screening, run-in, washout and both treatment periods. A 2-week diary was also completed during the washout period, although this did not provide data specific to the primary end-point. Qualified investigator study staff reviewed the diary data together with the patients/parents at subsequent visits and then transferred the diary data into the case report form (CRF).

To evaluate predictive variables for response, patient demographics such as gender, age and family history of PNE (yes/no) were collected at the initial screening visit by the investigator and recorded in the CRF. Maximum voiding volume and nocturnal diuresis (nocturnal urine volume divided by sleeping time) were calculated using diary data collected during a 2-day assessment over the last 2 days of the screening period. Parents were provided with voiding diaries and collection containers, which would allow them to measure volume (one for urine output and one for fluid intake). Specifically, patients were asked to record the volume and time of fluid intake and to record the volume and time of urination. At night, the child was woken up 1 h after bedtime and 5 h later (6 h after bedtime). During the daytime and during the night, the urine was measured using a measuring beaker. The time the child went to bed and the time the child got up the next morning were recorded for both days.

Assessments and statistical methods

The primary end-point of the study was patients' response to desmopressin calculated in terms of the percentage reduction in mean number of wet nights per week, from screening to the last 2 weeks of treatment (end of treatment; EOT), as recommended by the International Children's Continence Society (ICCS) (1). Secondary end-points included the mean number of wet nights per week at single 2-week intervals (detailed below), percentage of patients remaining dry after the washout period and predictive factors for response at EOT. Analyses were carried out on all available data, as well as excluding data from Canada. These subanalyses excluding Canada are presented in the tables and figures and were performed to investigate dosages of 0.2 and 0.4 mg independently of the 0.6 mg dosage, which was used in the Canadian arm of the study, but is not licensed in a number of countries.

Responses (percentage reduction) were subdivided into three categories: ≥ 90% reduction, 50–89% reduction (these two categories being combined to represent 'responders') and < 50% reduction. The last category also included patients for whom no reduction was calculated (if no 2-week period under treatment with ≥ 7 evaluable days was available).

The mean number of wet nights per week was also calculated for each patient during the screening period and for the 2 weeks corresponding to EOT. For each time interval, the mean number of wet nights per week was computed as: (number of wet nights/number of evaluable days) × 7 days.

A logistic regression model was used to investigate the relationship between response at EOT (i.e. ≥ 50% reduction in mean number of wet nights per week) and several possible predictive variables. The logistic regression model included the response at EOT as the dependent variable (excluding patients with missing response). The following factors were considered: country, gender, age, maximum voiding volume, nocturnal diuresis and family history of PNE (yes/no). Dose and duration of treatment were not included in the final analysis of predictive factors because they were not determined at baseline and therefore could not be used to predict success of desmopressin prior to starting treatment. Each additional variable was included in the model if its p-value was ≤ 0.1; otherwise, it was excluded from the following stages.

Treatment-emergent adverse events (TEAEs) were defined as all adverse events (AEs) that occurred after the first administration of treatment or existing AEs that worsened in intensity during the treatment period and were monitored throughout the study. TEAEs were categorised as mild, moderate or severe; the causal relationship between the drug and the AE was rated by the investigator as probable, possible, unlikely or unrelated by the investigator.

Response rates at EOT and 95% confidence intervals (CIs) were calculated according to the recommended method of Altman et al. (29). CIs were also calculated by gender, age group (5–8, 9–11, ≥ 12 years), final dose group (0.2, 0.4 and 0.6 mg) and by compliance during the first treatment period (taken as instructed, > 75% of tablets taken, 50–75% of tablets taken, < 50% of tablets taken).

Results

Patient disposition and baseline demographics/characteristics

In total, 936 patients were screened, 744 were enrolled and 471 (63%) completed the study (excluding Canada, $n = 539$ and 62% completed the study). The majority of enrolled patients were men (71%) and the mean age was 8.7 ± 2.5 years. A total of 51% had a family history of PNE. A summary of patient baseline demographics and characteristics is presented in Table 1. Patients had a median of 6 wet nights per week. A total of 70/720 (10%) patients with data received a final dose of 0.2 mg, 483/720 (67%) patients received a final dose of 0.4 mg and 168/720 (23%) patients received a final dose of 0.6 mg (all in Canada). Reasons for withdrawal included lack of efficacy (16%), other reasons not specified (11%), patient preference (8%) and AEs (2%).

Response to desmopressin at end of treatment

In the intent-to-treat (ITT) population, the overall proportion of patients achieving ≥ 50% reduction in wet nights per week from screening to EOT was 40.5% in the full sample (301/744) and 40.6% excluding Canada (219/539) (Table 2). It should be noted that the group achieving < 50% reduction in mean number of wet nights per week included 23/744 patients (3%) who failed to provide an evaluable response.

A summary of response status at single time intervals is shown in Figure 2. The response rate was the highest during the first and second treatment periods (37 and 39%, respectively). Some patients who showed ≥ 50% reduction in wet nights in the first treatment period dropped out during the second treatment period and therefore the percentage of patients responding by ≥ 50% overall is higher than that of patients responding during the individual treatment periods.

Table 1 Patient baseline demographics and characteristics

Variable	Overall *n* = 744
Men, *n* (%)	531 (71)
Women, *n* (%)	213 (29)
Age (years)	
n	744
Mean (SD)	8.7 (2.5)
Range	5–17
Height (cm)	
n	738
Mean (SD)	130.2 (14.1)
Range	96–183
Weight (kg)	
n	741
Mean (SD)	30.6 (11.7)
Range	14–98
BMI (kg/m^2)	
n	737
Mean (SD)	17.50 (3.39)
Range	11.8–36.4
Family history of PNE, *n* (%)	
n	744
Yes	377 (51)
No	323 (43)
NA or missing	44 (6)
Nocturnal diuresis (ml/min)	
n	697
Median	0.3190
Range	0.00–1.386
Maximum voiding volume (ml)	
n	708
Median	179
Range	30–1100
Wet nights/week	
n	739
Median	6
Range	2–7

BMI, body mass index; SD, standard deviation.

Table 2 Response status at end of treatment

Reduction in wet nights (%)	% (*n*)	% (*n*) excluding Canada
≥ 90% reduction	16.7% (124/744)	16.1% (87/539)
50% to < 90%	23.8% (177/744)	24.5% (132/539)
< 50% or missing	59.5% (443/744)	59.4% (320/539)
Total with ≥ 50% reduction (ITT population)	40.5% (301/744)	40.6% (219/539)
Total with ≥ 50% reduction (excluding missing data)	41.7% (301/721)	42.0% (219/521)
95% CIs	38.2, 45.4	37.9, 46.3

ITT, intent-to-treat; CIs, confidence intervals.

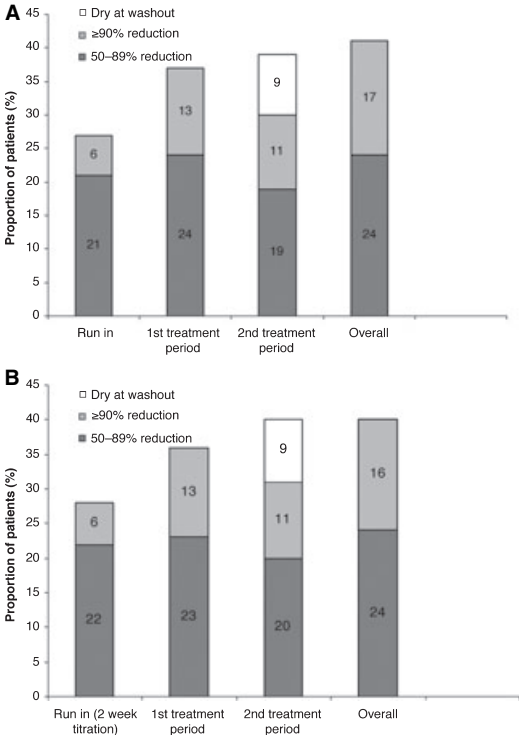

Figure 2 Response status at single time intervals and overall during the course of the study (A) for entire sample (*n* = 744), (B) excluding Canada (*n* = 539)

Statistical analyses of response at EOT by gender, age, final dose and compliance in the evaluable response dataset revealed similar rates of response (≥ 50% reduction) for male and female patients (41 vs. 44%). The percentage of patients achieving ≥ 50% reduction in wet nights by age, final dose and compliance, is shown in Table 3. The response at EOT increased with age and was more than doubled with a final dose of 0.2 mg compared with doses of 0.4 and 0.6 mg. It should be noted, however, that only patients with more resistant disease received higher doses. Response rates increased with greater compliance.

Mean number of wet nights per week

The mean number of wet nights per week at screening for the full sample was 5.52 ± 1.39 and this decreased to 3.68 ± 2.63 at EOT, a mean reduction of 1.83 ± 2.25 wet nights per week (median reduction was 1.50). Excluding Canada, patients had a mean of 5.38 wet nights per week at screening (± 1.44) and this decreased to 3.65 (± 2.62) at EOT, a reduction of 1.73 ± 2.20 wet nights per week.

Table 3 Response rate (≥ 50% reduction in wet nights per week) by age, dose and compliance [excluding missing data only (n = 721) and excluding Canadian data and missing data (n = 521)]

	% with ≥ 50% reduction in number of wet nights per week		% with ≥ 50% reduction in number of wet nights per week (excluding Canada)	
Variable	Total n = 721	95% CIs	Total n = 521	95% CIs
Age				
5–8 years	33.5 (137/409)	29.1, 38.2	34.2 (103/301)	29.1, 39.7
9–11 years	47.5 (95/200)	40.7, 54.4	48.3 (69/143)	40.2, 56.4
≥ 12 years	61.6 (69/112)	52.4, 70.1	61.0 (47/77)	49.9, 71.2
Dose				
0.2 mg	88.6 (62/70)	79.0, 94.1	92.2 (47/51)	81.5, 96.9
0.4 mg	37.7 (182/483)	33.5, 42.1	36.6 (172/470)	32.4, 41.0
0.6 mg	33.9 (57/168)	27.2, 41.4	N/A	N/A
Compliance				
Taken as instructed	46.6 (231/496)	42.2, 51.0	46.5 (182/391)	41.7, 51.5
> 75% of pills	46.2 (48/104)	36.9, 55.7	43.6 (24/55)	31.4, 56.7
50–75% of pills	27.8 (5/18)	12.5, 50.9	22.2 (2/9)	6.3, 54.7
< 50% of pills	25.0 (5/20)	11.2, 46.9	25 (3/12)	8.9, 53.2
Unknown	14.5 (12/83)	8.5, 23.6	14.8 (8/54)	7.7, 26.6

CIs, confidence intervals.

Figures 3 and 4 summarise the reduction in wet nights per week by age and final dose, respectively.

Patients achieving complete dryness

The proportion of patients who remained dry during the treatment-free (washout) period was 9% (64/744) : 6% (12/192) in the UK; 7% (15/205) in Canada; 10% (22/213) in Germany and 11% (15/134) in France.

Possible predictive factors for response

Using the full sample (excluding missing data) in the model for predictive factors for response, age ($p < 0.0001$), maximum voided volume ($p = 0.0040$) and nocturnal diuresis ($p < 0.0001$) fulfilled the criterion of $p \leq 0.1$ for inclusion into the final model. In this model, increased age [odds ratio (OR) = 1.09 per year; 95% CI: 1.02, 1.17; $p = 0.017$] and nocturnal diuresis (OR = 1.34 per ml/10 min; CI: 1.20, 1.50; $p < 0.0001$) statistically significantly predicted an increased response to desmopressin. In clinical terms, this means that for a 60 ml increase in nocturnal diuresis over a 10-h period, the OR of response to desmopressin increases from 1 to 1.34. Therefore, greater nocturnal diuresis and increased age were both predictive of a better response to desmopressin treatment. When Canadian data were excluded from the analyses, nocturnal diuresis ($p < 0.0001$) remained a significant predictor of response, but age showed only a trend for association ($p = 0.087$).

Safety evaluation

Overall, 222 (30%) patients experienced TEAEs (Table 4). A total of 5% of patients experienced TEAEs that were judged as related to study medication (Table 5). The most common complaints judged as related to study medication were abdominal pain not otherwise specified (4/744, 1%), upper abdominal pain (6/744, 1%) and headache (8/744, 1%). In total, 30/744 (4%) patients discontinued study medication because of a TEAE and 16/744 (2%) patients withdrew from the study because of a TEAE. The TEAEs that led to withdrawal were classed as either mild or moderate. None was a serious event and 13/20 were possibly or probably related to study medication. The rate of treatment-related AEs was similar for all age groups (5–8 years, 5%; 9–11 years, 4%; ≥ 12 years, 7%).

Discussion

Numerous controlled trials have demonstrated the efficacy of desmopressin in the treatment of PNE (18). This study is the largest evaluation to date of the effect of long-term (up to 6 months) treatment with desmopressin in the 'real-life' setting of unselected, treatment-naïve patients,

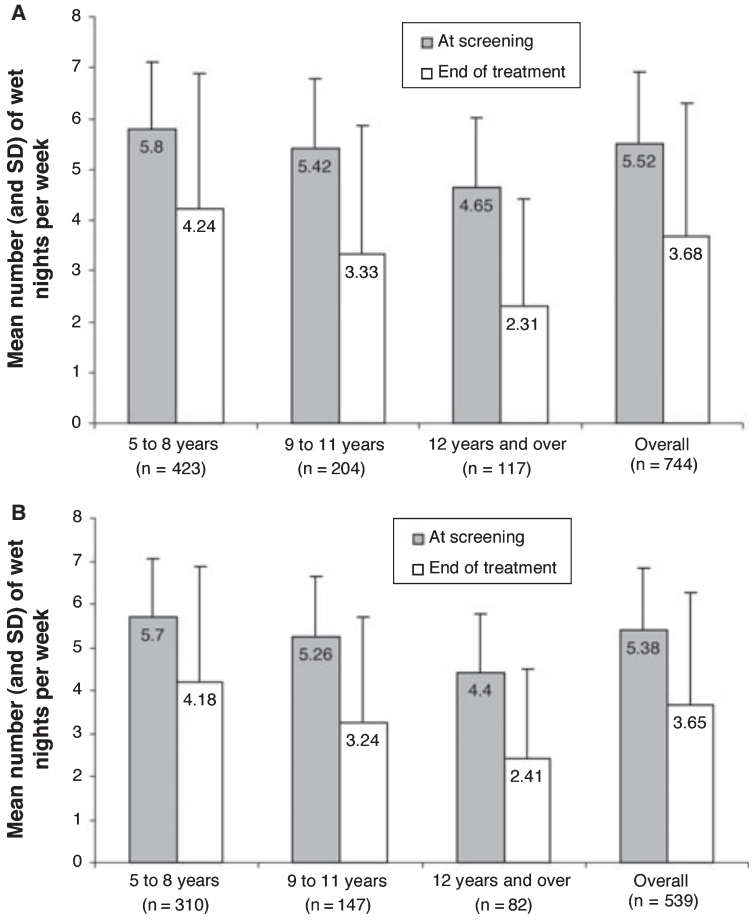

Figure 3 Mean number of wet nights (and standard deviation) per week by age (A) for entire sample (n = 744), (B) excluding Canada (n = 539)

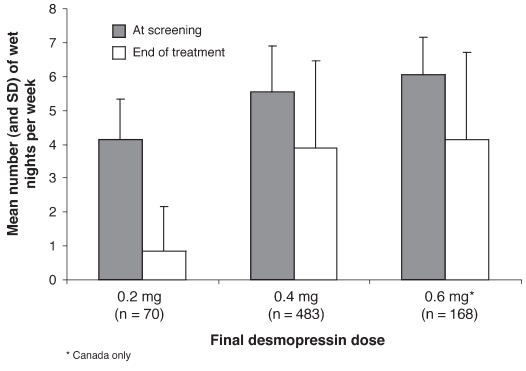

Figure 4 Mean number of wet nights (and standard deviation) per week by final dose. Note that the dose was only increased for those patients who did not respond at the lower dose, and the 0.6 mg dose was only available in Canada

representing those seen in clinical practice in four different countries.

Patients included in the study had severe PNE with a median of 6 wet nights per week, far above the threshold for inclusion of 3 wet nights per week during screening. The number of wet nights experienced was at least halved at the end of desmopressin treatment in 40.5% of participants in the ITT population and response was consistent across countries and genders. The success of desmopressin in relieving PNE in a substantial proportion of patients is therefore confirmed. The rate of response to desmopressin reported in previous trials where desmopressin is used as first-line treatment has sometimes been higher [60–70% response (16,17,30,31)] than in this study. This difference may in part be attributable to the fact that enuresis in this patient pool was severe, which may cause the strength of response to be lower as some studies have found desmopressin to be most effective in those patients with fewer baseline wet nights (24). Furthermore, children in this study may not have been exclusively monosymptomatic, although obvious signs of overactive bladder (OAB) were taken into account. It is possible that there were still some children who drank more in the evenings to compensate for OAB included in

Table 4 Summary of all treatment-emergent adverse events experienced by ≥ 2% of patients

	n = 744	
System organ class	***n* (%)**	**Events**
All TEAEs (≥ 2%)	222 (30)	404
Gastrointestinal disorders	73 (10)	89
Abdominal pain upper	14 (2)	15
Diarrhoea	13 (2)	14
Gastroenteritis	13 (2)	13
Vomiting	22 (3)	24
General disorders and administration site conditions	16 (2)	18
Pyrexia	13 (2)	14
Infections and infestations	71 (10)	91
Influenza	16 (2)	16
Nervous system disorders	29 (4)	36
Headache	28 (4)	35
Psychiatric disorders	12 (2)	12
Respiratory, thoracic and mediastinal disorders	59 (8)	85
Nasopharyngitis	21 (3)	27
Pharyngitis	15 (2)	15
Skin and subcutaneous tissue disorders	17 (2)	20

TEAEs, treatment-emergent adverse events.

Table 5 TEAEs classed as possibly or probably related to desmopressin treatment

	n = 744	
System organ class	***n* (%)**	**Events**
All drug-related TEAEs	25 (3)	42
Gastrointestinal disorders	12 (2)	13
General disorders and administration site conditions	2 (< 1)	2
Investigations	1 (< 1)	1
Musculoskeletal and connective tissue disorders	2 (< 1)	6
Nervous system disorders	5 (1)	8
Psychiatric disorders	4 (1)	4
Renal and urinary disorders	3 (< 1)	4
Respiratory, thoracic and mediastinal disorders	2 (< 1)	2
Skin and subcutaneous tissue disorders	1 (< 1)	1
Vascular disorders	1 (< 1)	1

TEAEs, treatment-emergent adverse events.

the study and therefore experienced more wet nights during treatment than might be expected in monosymptomatic PNE. Indeed, the median maximum voiding volume was 179 ml, with a range of 30–1100 ml. This suggests that a proportion of the study population had a reduced functional bladder capacity, possibly associated with OAB, but that overt OAB symptoms might have been masked by poor fluid intake during the day. Unfortunately, as a fixed drinking load was not used during the screening phase of the study, the presence of OAB in a subgroup of patients can only be hypothesised.

Another possible reason for discrepancies in response rates across studies may be the differing criteria for 'response' and 'non-response' that have been used. The latest ICCS guidelines (1) suggest that criteria for 'response', 'partial response' and 'non-response' should be standardised, and that non-response should be defined as < 50% decrease in wet nights per week. However, this is a conservative cut-off, and it is likely that smaller improvements, of any appreciable order of magnitude, are rewarding for the individual patient and the family concerned. It may therefore be of use to evaluate each child's response on an individual basis rather than grouping into these broad categories and to continue desmopressin treatment for an extended period, alone or in combination with other therapies such as alarm, as appropriate.

Overall, however, a large number of patients experienced a considerable reduction in wet nights with desmopressin treatment. For those patients who achieved ≥ 50% reduction in wet nights in this study, efficacy for many began almost immediately, with children demonstrating an improvement in symptoms during the 2-week run-in period. The number of patients responding to treatment increased with each period of treatment, however, which suggests the value of persisting with desmopressin treatment to attain the most successful outcome for each child.

This study has also provided evidence for the tolerability of up to 6 months' desmopressin treatment (with a treatment-free break between 3-month periods). The tolerability profile was consistently good over all age groups and over the length of the treatment period. This indicates the tolerability of continued treatment with desmopressin, where appropriate.

Given that some patients are resistant to desmopressin treatment, one of the principal intentions of this study was to investigate whether any factors could be identified that might predict which patients are most likely to respond well to desmopressin. It was found that treatment became more efficacious with increased nocturnal diuresis and increased age of the child (when Canadian data were included).

These findings therefore suggest that it may be of value for physicians to evaluate diuresis when setting up a treatment regimen for individual patients. Analysis revealed that a 60 ml increase in nocturnal diuresis over a 10-h period increased the OR of response to desmopressin from 1 to 1.34. Increased age also predicted a stronger response to desmopressin, with around 50% of children > 8 years responding to treatment. The increased efficacy seen in older children is supported by findings from previous smaller studies (24,32). The reason for the association is as yet unclear, but may relate to the fact that younger children are more prone to have small voided volumes and/or bladder overactivity, which is linked to inadequate desmopressin response (33). However, as PNE tends to become more severe with age (13,34), it may be appropriate to treat bedwetting early when PNE is less severe and the negative psychological impact of unresolved PNE can be avoided. As approximately one-third of 5–8 year olds responded to treatment in this study, which is much higher than would be predicted by spontaneous resolution (5–7.5% of patients over 6 months), pharmacological intervention in younger children may be warranted.

Gender, country and family history of PNE were not predictive of response to desmopressin treatment. The lack of an association with gender is supported by other studies, which have failed to find an effect of gender (24,35). The fact that children in each country achieved similar rates of response to desmopressin is perhaps not surprising, although there is evidence to suggest that some populations, such as ethnic Chinese children in Hong Kong (36), may have higher rates of response to desmopressin than others, possibly because of a genetic influence on response. However, in this study, there was no evidence of an effect of heredity on response to desmopressin treatment. Several other studies support this lack of an association with family history of PNE (27,37), although this does not rule out a genetic effect on differences between ethnic populations in rates of response to PNE treatment.

Although maximum voided volume (formerly termed 'maximum functional bladder capacity') was predictive of response to desmopressin in early logistic regression models in this study, it was not found to predict significantly response to desmopressin in the final model, when age and nocturnal diuresis were included. Other studies have reported an association between response to desmopressin and bladder capacity/voiding volume (24,32), but these did not assess nocturnal diuresis specifically. If nocturnal diuresis had been included as a variable, this may have led to bladder capacity being dropped from the predictive model in these studies also. Maximum voided volume and nocturnal diuresis should be evaluated to assess their importance in individual cases.

Results from this study may also guide clinical practice during ongoing desmopressin treatment, as they indicate an association between good compliance and good patient outcome. It is likely that this is influenced by a positive feedback loop, whereby adherence to treatment increases its efficacy and hence patients are more motivated to adhere to treatment. Physicians may also optimise success of desmopressin treatment if, at the outset, they explicitly encourage patients to persist with medication even if results are not immediate. Prescription of the oral lyophilisate formulation of desmopressin, recommended by the European Medicines Evaluation Agency as the formulation of choice for the paediatric population (38), may facilitate greater compliance, especially in younger children (39). In this study, lower doses of desmopressin were also associated with a greater reduction in wet nights. However, these data should be interpreted with some caution, as it is a feature of the study design that those patients who responded well to low doses were excluded from the group of patients for whom medication was uptitrated. The group receiving high doses of desmopressin was consequently selected for children with more treatment-resistant PNE. Uptitration of desmopressin may therefore still be beneficial for children whose bedwetting does not improve with lower doses.

Overall, this study focusing on severe cases of PNE confirms and extends current understanding of the efficacy, safety and likelihood of success of long-term desmopressin treatment in these children. Further data collection and analyses are planned for the 6-month follow up after the treatment period and this information will provide valuable additional insights into the maintenance of improvements in enuresis after cessation of medication.

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Author contributions

Authors Henri Lottmann, Lola Baydala, Paul Eggert and Jonathan Evans were the lead clinical investigators recruiting patients and co-ordinating data collection in France, Canada, Germany and the UK, respectively. Bjarke Mirner Klein provided statistical analyses for the paper and Jens Peter Norgaard contributed to the design and co-ordination of the overall project and its funding. All authors contributed to the interpretation of the data, reviewed the manuscript and approved the final draft for submission.

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