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Comparative Tolerability of Drug Treatment for Nocturnal Enuresis in Children

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Abstract

Primary nocturnal enuresis is one of the most frequent complaints in paediatric and urologic practice. Physicians face the dilemma of whether or not to treat primary nocturnal enuresis since the trend towards spontaneous remission is countered by social disadvantages and reduced self esteem of the children affected and their families. We reviewed randomised, controlled trials investigating efficacy and adverse effects of current medical treatment for primary nocturnal enuresis. Only desmopressin and imipramine displayed significant effects in reducing wet nights: when compared with baseline bedwetting or placebo controls, 30–70% of the studied children achieved therapeutic success. For drugs such as indometacin or oxybutynin, convincing studies displaying a significant positive effect are still needed. However, considering the adverse effects profiles of desmopressin and imipramine it can be seen that imipramine is associated with about twice as many unwanted reactions. More importantly, a serious adverse

effect of imipramine is sudden cardiac arrest. In general, adverse effects with desmopressin are rare and mild, but there have been a number of case reports of hyponatraemic hypervolaemia associated with coma and seizures. Of these, many cases were attributed to excess water intake before taking the drug and all children recovered fully. In summary, if medical treatment is considered, preference should be given to desmopressin.

1. Voiding Disorders in Children

In contrast to adults, the urinary tract in children is still developing, not only in terms of size and capacity but also in terms of involuntary and voluntary control by the nervous system. The range of developmental capabilities is subject to great variation, especially in younger children and this variation reduces as children get older. This fact posses problems for the physician who has to decide whether a certain disorder in a child requires treatment or if the patient just lies within the lower range of normal development. Furthermore, since different systems do not mature simultaneously, the pattern of disorders itself shows great variation. In 1998, Norgaard and coworkers, on behalf of the international children's society, set up a classification for disorders associated with urinary incontinence.[1] In this classification, urinary incontinence was separated into: (i) urge syndrome with dysfunctional voiding; (ii) urge syndrome with urge incontinence; (iii) dysfunctional voiding; and (iv) wetting in attention deficit disorders. By signs and symptoms, these disorders were clearly separated from the condition of nocturnal enuresis. Likewise, medical and nonmedical treatments are fundamentally divergent.

2. Nocturnal Enuresis

Nocturnal enuresis is one of the most frequent complaints in paediatric and urologic practice. At the age of 5 or 6 years, an age when most children start school, a child is expected to control diurnal and nocturnal bladder and bowel function. If nightly bedwetting persists beyond this age, with a frequency of at least two episodes per week, the condition is classified as primary nocturnal enuresis. In contrast, if nocturnal enuresis is encountered after the child has achieved dryness for at least duration of 6 months, the condition is referred to as secondary nocturnal enuresis. Although this time interval lacks any scientific basis, the re-appearance of nocturnal enuresis itself is often associated with psychological life events such as parental divorce or school changes and has been proven to be a clinically useful tool.[2] The diagnosis of primary nocturnal enuresis can only be made after the appropriate exclusion of nephrologic (e.g. nephrogenic diabetes insipidus), urologic (e.g. unstable bladder, urinary tract infections), psychiatric or endocrinologic (central diabetes insipidus) disorders. Besides the above-mentioned diagnostic criteria, which are sufficient to establish the diagnosis, frequently encountered associated symptoms are a very deep sleep (i.e. the children do not wake up around the episode of bedwetting) and in about 50–60% the parents report that they also did wet their beds at younger age.[3] The cross-sectional study of Byrd and colleagues (including 10 960 children) revealed that 3% of all girls and 7% of all boys experience primary nocturnal enuresis at the age of 7 years if the abovementioned criteria are used.[4]

Ideas on the aetiology of primary nocturnal enuresis have undergone astonishing changes over the course of time. At first, attention was focussed mainly on the conspicuously deep sleep of the enuretic patients. Trousseau was one of the first researchers to derive the hypothesis of 'sleep enuresis' from his observations.[5] As a result, nocturnal enuresis, like sleep walking or 'pavor nocturnus', was classified with the parasomnias. The goal of therapy was therefore to influence sleep. The success of therapy with tricyclic antidepressants (TCAs) appeared to confirm this hypothesis of a central genesis of primary nocturnal enuresis. Peripheral effects of TCAs were used much later to explain the reasons for the benefits seen with TCAs in primary noctur-

nal enuresis. At the end of the 1970s, a fundamentally different hypothesis prevailed. It was based on the findings of reduced nocturnal antidiuretic hormone (ADH) secretion and the consecutive increase in nocturnal urine production.[6] Accordingly, bedwetting occurs when the functional bladder volume is exceeded. From daily clinical experience, however, it is evident that it is pointless to restrict the evening fluid intake of patients with primary nocturnal enuresis or wake them during the night to take them to the lavatory. Countless parents with enuretic children have tried this – and failed. If the aims of therapy were to reduce the nocturnally increased urine volume, then these simple measures should be just as effective as drug-induced reduction of excretion.

In addition to the known renal vasopressin receptor mediated renal effect of desmopressin, in recent years evidence for a central effect of this agent has increased.[7] In a prospective, randomised, double-blind, crossover study it has been shown that desmopressin has an positive effect on short-term memory in children undergoing treatment for enuresis.[8] Earlier studies have already demonstrated the effect of vasopressin and its metabolites on the CNS in humans.[9]

It has also been pointed out recently that a subgroup of children with nocturnal enuresis experiences a reduced nightly functional bladder volume, a circumstance that is probably often missed by routine examinations. Moreover, it has been suggested that reduced nightly functional bladder capacity is an important cause of refractory nocturnal enuresis.[10,11]

In general, the prognosis of primary nocturnal enuresis is excellent. The spontaneous rate of remission is about 15% per year, so that by puberty almost all children achieved complete dryness.[12] However, the remaining 1% is likely to have persisting primary nocturnal enuresis throughout life. At present, there is no prognostic parameter that correlates with the age at which a child with primary nocturnal enuresis may achieve continence.

Considering these excellent remission rates, it seems reasonable to consider primary nocturnal enuresis as a maturational delay rather than as a disease. In practice, physicians face the dilemma, whether a child with a disorder that will fade with time, and which is by no means life-threatening, needs any medical treatment at all. However, several studies have revealed the considerable social and emotional burden in these families, which also needs to be considered.[13] For instance, lowered self-esteem in children with primary nocturnal enuresis might lead to a decreased school performance, which in turn could have further and considerable long-term consequences.[14,15]

In this review, we seek to evaluate pharmacological treatments for primary nocturnal enuresis, and compare their efficacy and safety profiles. By applying the principles of critical appraisal we sought to primarily select clinical trials conducted in a randomised and controlled manner (level A evidence) that included patients with the above mentioned criteria. A search of PubMed was performed using the following search terms, either singly or in combination: ‘nocturnal enuresis’, ‘treatment’, ‘review’, ‘desmopressin’, ‘ddavp’, ‘imipramine’, ‘tricyclic antidepressants’, ‘children’, ‘side effects’, ‘adverse reaction’, ‘prospective’, ‘randomized’, ‘controlled’. In every publication revealed by this search strategy, the reference section was used to identify publications not listed in PubMed. We did not investigate other commonly used and successful forms of non-medical treatment, such as the alarm pad. Its effectiveness has been thoroughly investigated by Glazener and colleagues in a recent Cochrane review.[16]

3. Desmopressin

Desmopressin (1-deamino-cys-8-D-arginine-vasopressin), is a synthetic analogue of the endogenous hormone arginine vasopressin (AVP), also known as ADH. The hypothalamic peptide ADH serves as a water retaining hormone by mediating renal water reabsorption. Desmopressin was initially developed for the treatment of patients with central diabetes insipidus, which is characterised by the lack of endogenous AVP, which can be congenital or acquired (e.g. brain tumours). As a consequence,

water cannot be absorbed in the renal collecting duct via the AVP-receptor 2 (AVPR2)/aquaporin-2 (AQP2) system so that affected patients produce large amounts of unconcentrated urine. AVPR2 mutations are associated with X-linked nephrogenic diabetes insipidus whereas AQP2 mutations cause either an autosomal recessive or the even rarer autosomal dominant form of nephrogenic diabetes insipidus.[17-19] The supplementation of desmopressin intranasally, subcutaneously or intravenously, corrects this deficit and restores normal renal concentrating ability. In contrast, patients with nephrogenic diabetes insipidus, due to a loss-of-function mutation in the AVPR2/AQP2 system are also unable to concentrate their urine but display high endogenous levels of AVP and are hence unresponsive to the administration of desmopressin. Interestingly, the AQP2 gene has been excluded as a candidate for primary nocturnal enuresis.[20]

3.1 Efficacy

3.1.1 Intranasal Application

The antidiuretic properties of desmopressin led to its first use in primary nocturnal enuresis in the late 1970s.[21] Since then, the drug has been approved for intranasal and oral administration in the treatment of primary nocturnal enuresis. Interestingly, dosage recommendations have for a long time been imprecise suggesting one to four puffs of the nasal spray before going to bed, which corresponds to 10–40μg. The usual paediatric dosage recommendations, as related to bodyweight, height or body surface area, are not standardly introduced. However, a recent study, showed that the formula: $\mu g = 0.8 \times kg$ bodyweight/age (years), allows the calculation of a dose that was found to reduce wet nights by 50% in 80% of all patients.[22] An increase of the calculated dosage was found only beneficial in an additional 5% of patients. Such studies for the oral administration of desmopressin are currently not available.

By performing a literature search, we identified ten randomised, double-blind, crossover studies in which at least one arm included a placebo control group. A total of 370 children were treated in at least one arm of the study with intranasal desmopressin.[8,23-32] In all but one study there was a significant reduction in wet nights compared with either baseline or to the wet nights registered in the control group.

3.1.2 Oral Application

The oral formulation of desmopressin was developed in order to overcome the inconsistent therapeutic effect during (acute and chronic) rhinitis as well as the nasal discomfort during application, and finally to overcome the disadvantage of having to keep the nasal spray at 4°C (a formulation which is stable at room temperature has been approved just recently). By oral application the standard dosage of desmopressin is about ten times higher when compared with the intranasal application (200–600 μg/day). Four placebo-controlled, double-blind, crossover studies were identified in which at least one arm of the study was treated with oral desmopressin.[33-35] These studies included a total of 157 children. All studies reported a significant decrease in wet nights with oral desmopressin compared with the controls. Concerning the mode of application, there is currently no convincing evidence for the superiority of either oral or intranasal desmopressin treatment, neither for efficacy nor for adverse effects.

3.1.3 Long-Term Use (>4 Weeks)

Desmopressin was initially approved for short-term interventions only (<4 weeks). Although some studies report about stable dryness after discontinuation of the treatment in some patients, there is currently no clear evidence showing that the beneficial effect of desmopressin continues beyond the end of the treatment.[36] Accordingly, the long-term use of desmopressin could provide a therapeutic option to prevent the recurrence of nocturnal enuresis and its associated stress on the children and their families. Fourteen controlled studies have been performed, three included a crossover design.[23,29,35-47] In one of these long-term studies, Rittig et al. investigated desmopressin treatment for 24 weeks and found a significant improvement in the active treatment group.[29] The other studies also showed a beneficial effect comparable to the short-term results. There was no evidence that dosage adjustments were nec-

essary once a therapeutic optimal dosage was found. A large Swedish study, including 399 children in a intention-to-treat cohort demonstrated a reduction of wet nights by at least 50% for nearly two-thirds of the patients (61%) receiving 20–40μg of intranasal desmopressin.[48] In an open, non-randomised, multicentre trial, Chiozza et al. found desmopressin to be effective in 70–75% of a total of 237 children treated with different regimens of intranasal application ranging from of 20–40μg.[49]

3.2 Safety

The literature search with regard to the safety of desmopressin treatment was restricted to placebo-controlled studies. Studies not mentioning adverse events were excluded. In total, we analysed 12 short-term studies (<4 weeks) including 703 children and eight long-term studies (>4 weeks) including 616 children.[8,24-27,29,35,40,41,43,44,46,47,50-54] Headache, gastrointestinal symptoms and nasal discomfort were the most frequently mentioned adverse events. Nasal irritation and nose bleeding were reported for intranasal application, and might either be related to the irritating effect of the drug or to the application tool itself.

In order to assess the magnitude of adverse events with desmopressin versus placebo, we pooled the data to calculate the number of adverse events per patient. However, it should be noted that adverse events were described in the studies as total numbers, not per patient, so patients could have experienced more than one adverse event, thus distorting our findings.

We found that there were 12.3 events per patient during short-term treatment and 11.6 events in long-term treatment which in summary gave a mean of 12% adverse events in all patients treated (table I). The combined adverse event rate for all the placebo arms of the included studies was 3%. Analysing this data in more detail, it became apparent that most of these adverse events were minor and even resolved as treatment continued. For the two severe events recorded (atopic dermatitis and anorexia) the data provided are too limited to draw any conclusions. Comparing short-term versus long-term treatment, there was in principle no difference in the pattern of adverse events, nor did the rate of such increase with duration of the study. In a review by Glazener and Evans, an average of 5.3 adverse effects per 100 children treated were reported.[36]

Table I. Number of adverse events (%) seen in short- and long-term randomised, placebo-controlled studies of desmopressin in primary nocturnal enuresis

Adverse event	Desmopressin		Placebo total
	long-term (>4 wks) [n = 616]	short-term (<4 wks) [n = 703]	(n = 1019)
Nasal discomfort	16 (2.6)	8 (1.1)	5 (0.5)
Epistaxis	0	6 (0.9)	0
Nausea	0	5 (0.7)	0
Vomiting	2 (0.3)	3 (0.4)	1 (0.1)
Headache	21 (3.4)	18 (2.6)	10 (1)
GI symptoms	0	23 (3.2)	5 (0.5)
Cough	18 (2.9)	15 (2.1)	2 (0.2)
Rhinitis/ pharyngitis	12 (1.9)	3 (0.4)	11 (1.1)
Back pain	0	1 (0.1)	0
Rash	1 (0.2)	0	0
Anorexia	1 (0.2)	0	0
Atopic dermatitis	1 (0.2)	0	0
Fever	0	5 (0.7)	2 (0.2)

GI = gastrointestinal; **wks** = weeks.

Probably the most dreaded although rare complication of desmopressin therapy is hyponatraemic hypervolaemia, which can lead to seizures and coma. This event was not encountered in any of the controlled studies. This could be due to the relatively small number of patients studied in clinical trials compared with the total number of children treated in the 'real world'. A number of case reports of hyponatraemic hypervolaemia have been published, emphasising that this dramatic adverse effect is not too uncommon and it can be anticipated that the occurrence of this adverse effect is higher than reported. Hjålmas and Bengtsson reviewed the literature from 1974–1992 and found 21 reports on water intoxication after desmopressin treatment.[55] In 1996, Williford and Bernstein reported on a 29-year-old woman with water intoxication due to desmopressin administration for nocturnal enuresis and reviewed data for an additional 11 paediatric and two adult patients.[56] Since then, at least 16 more cases have been reported.[57-70] There was no

correlation to age, sex, and fluid intake before going to bed or dosage of desmopressin administered. Furthermore, there was no obvious correlation between duration of treatment and onset of the event. Most cases were children, and all cases recovered completely without remaining sequelae. However, one fatality occurred in an adult.[69] Wieting and colleagues reported on a 7-year-old boy who displayed CNS ischaemia after varicella infection while being treated with desmopressin for nocturnal enuresis.[71] The authors point out the pro-coagulatory effects of desmopressin. In a placebo-controlled, short-term study, Janknegt and Smans investigated blood pressure as well as haematological and serum electrolyte values and found no difference between the study groups.[27] However, they found a significant increase in bodyweight in the desmopressin group, consistent with the antidiuretic action of desmopressin. However, they did not find a significant difference in morning urinary osmolality between the groups. The study of Yap et al. also looked at bodyweight and electrolyte values, but failed to detect significant differences.[47] In view of the serious consequences of hyponatraemic hypervolaemia, it seems indisputable to accurately inform the parents to restrict water intake and keep tightly to the dosage prescribed by the treating physician. Interestingly, desmopressin achieves its therapeutic effect at a supraphysiologic dosage. Whereas a maximal dose of two intranasal applications of 5μg each is sufficient for treating central diabetes insipidus, single evening doses of up to 60μg are needed to achieve a result in primary nocturnal enuresis. Thus, use of this therapy has been accompanied by constant concerns about adverse effects related to use of a high dosage, but without justification, as the data presented here suggest. An exceptionally higher prescribed dose or accidental overdose has not been reported in publications describing hyponatraemic hypervolaemia.

4. Tricyclic Antidepressants

TCAs are readily absorbed from the gastrointestinal tract and are rapidly available in the circulation. TCAs cross the blood-brain barrier and act on the CNS. Their mode of action works via blocking of noradrenaline and serotonin reuptake (α-receptors) from the synaptic gap into the corresponding neurones. Additionally, and of unknown relevance for the treatment of nocturnal enuresis, TCAs exhibit peripheral effects: anticholinergic action leads to lowering of the detrusor muscle tonus. On the other hand, the tonus of the M sphincter internus is increased. TCAs used for treatment of nocturnal enuresis include imipramine, amitriptyline, dosulepin (dothiepin), doxepin, trimipramine, clomipramine, desipramine, lofepramine, nortriptyline and protriptyline, the first two being those almost exclusively prescribed. As for desmopressin, TCA dosage recommendations with regard to bodyweight or body surface area are not common. Most studies use dosages according to age of the children, for instance ranging from 10–75mg in the case of imipramine. It must be mentioned, however, that the availability of many drugs in fixed amounts (e.g. tablets) is a general problem in paediatrics. This problem often prohibits the exact administration of the calculated dosage. Fritz et al. demonstrated a positive correlation between increasing dosage of imipramine and reduction of wet nights (maximum 2.5 mg/kg).[72] Imipramine should not be administered to children aged <6 years and the duration of treatment should be limited to 3 months.[73]

4.1 Efficacy

MacLean introduced TCAs for the treatment of nocturnal enuresis, based on the hypothesis that enuretic patients have some form of depression.[74] Since then several studies have been performed, testing various TCAs with or without additional treatments like psychotherapy, or drugs other than TCAs. We identified 11 placebo-controlled studies in which at least one arm contained imipramine and one placebo.[75-85] Most of the studies had no crossover design. In these studies, at total of 386 children were treated solely with imipramine (excluding the study arms with other treatments than imipramine and placebo). Dosages ranging from 10–75mg were administered in most of the studies at bedtime or twice daily in one trial. There was a significant

reduction of wet nights when compared with baseline values in all of the studies. On average, the reduction of wet nights was about 50%; however, this effect did not exceed the expected spontaneous cure rate after the drug was discontinued. Interestingly, five studies documented a significant positive effect of placebo. In the study of Ingle and Panase, placebo showed an even more sustained effect after discontinuation of the drug, when compared with imipramine.[86] Interestingly, this placebo effect was much more pronounced than in the placebo-controlled interventional studies for desmopressin. Fernández de Gatta and coworkers administered doses of 12.5–100 mg/day and reported an average decrease in wet nights of 71 ± 31% compared with baseline.[87] They studied the factors influencing the response to the treatment and found by regression analysis multiple factors like dose, total serum level, metabolite serum level, but also age and compliance as predictors of favourable outcome which could confirm by multivariant analysis. However, this study was not controlled and contained a mixed (primary and secondary nocturnal enuresis) population.

4.2 Safety

Of the above-mentioned placebo-controlled studies, only seven out of 11 mentioned adverse events, so only limited information is available. Using additional information from non-placebo-controlled studies or studies also including diurnal enuresis/encopresis, a more extensive overview of adverse events in 480 participants was undertaken.[88-90] Based on this data, an average 17.3 adverse events per 100 patients were calculated.[91] It seems more accurate to stratify for imipramine-only treated (n = 246) patients as well as for placebo-only-treated patients (n = 206) [table II]. This results in 83 adverse events per 246 patients treated (34 per 100 patients), thereby doubling the rate of unwanted effects; however, the same limitations of the data apply as for desmopressin. The gastrointestinal symptoms are possibly attributable to the anticholinergic effect. The high frequency of neurological adverse events is of particular concern in children, as the CNS is still developing. Moreover, since 1990, at least nine cases of imipramine-related sudden deaths in children have been reported.[92-98] These deaths reported in the literature have been attributed to sudden cardiac arrest since the children did not display any abnormal behaviours prior to dying. The studies of Fletcher et al. and Wilens et al. revealed consistent, although probably not clinically relevant ECG abnormalities in patients treated with TCAs.[99,100] From the cases reported so far, the daily administration of imipramine showed a tendency towards higher dosages. This stresses once more the need to establish weight and body surface area-dependent dosages for medications used in childhood. The study of McFee and colleagues for instance showed that even dosages of 9.4 mg/kg did not lead to symptoms of intoxication.[101] In summary, there is currently no parameter predicting the risk of a child experiencing cardiac symptoms which would point to a role for pharmacogenomics in terms of different genotypes of cytochrome P450 2D6. It appears that 'slow metabolisers' could be at greater risk of achieving high plasma levels of the drug than 'fast metabolisers'. Of note is also the

Table II. Adverse events seen in randomised, placebo-controlled studies of imipramine treatment in primary nocturnal enuresis

Adverse events	No. of events with imipramine (n = 206)	No. of events with placebo (n = 246)
Neurological events		
Lethargy	5	
Dizziness	5	1
Headache	5	
Depression	1	
Irritability	11	
Sleep disturbances	16	
Anxiety	10	
Nightmares		1
Other events		
Gastrointestinal symptoms	26	NR
Epistaxis	1	NR
Postural hypotension	1	NR
Rash	NR	2
Anorexia	3	NR

NR = not reported (in the particular study it was not mentioned if this adverse effect was investigated).

observation of Gire and coworkers, who described an imipramine withdrawal syndrome in a child who was treated with imipramine for nocturnal enuresis.[102]

5. Miscellaneous Pharmacological Treatments

5.1 Oxybutynin

Oxybutynin, a drug with anticholinergic effects, has been successfully used for bladder instability and/or sphincter-detrusor-dyssynergy. Its role in the treatment of primary nocturnal enuresis, which excludes these organic abnormalities, is unclear. Lovering and colleagues found that oxybutynin 10mg did not reduce the number of wet nights when compared with placebo.[103] Moreover, 5 of the 30 participants reported gastrointestinal symptoms, dizziness, fatigue, headache and dry mouth. Varan and colleagues compared the effectiveness of oxybutynin with indometacin and pseudoephedrine in primary nocturnal enuresis.[104] Oxybutynin did not reduce the number of wet nights. Five out the nine patients treated with oxybutynin experienced adverse events similar to the events seen in the study of Lovering et al.[103]

5.2 Prostaglandin Synthesis Inhibitors

Indometacin, a potent prostaglandin synthesis inhibitor, is an NSAID. In a double-blind crossover study, Al-Waili found a reduction of wet nights in 14 of 19 patients receiving indometacin; however, baseline measurements were not systematically done.[105] Common adverse events were headache, dizziness and gastrointestinal symptoms. In the above-mentioned study, indometacin did not reduce the number of wet nights.[104]

The effect of diclofenac was compared with desmopressin and placebo in a recent study involving a total of 62 participants in the treatment groups. Desmopressin (10.5–24.5μg) was effective in 85% of the cases and diclofenac (1 mg/kg bodyweight) in 33%. Adverse reactions were not mentioned.[106]

5.3 Carbamazepine

In a recent randomised, double-blind, placebo-controlled crossover study (n = 26), Al-Waili found that carbamazepine significantly ($p < 0.001$) reduced wet nights, while adverse reactions were not noticed.[107] Serum electrolytes and other laboratory tests remained normal. Further trials with greater patient numbers will be necessary to prove a sustained beneficial effect with regard to possible adverse effects.

6. Conclusion

This review of the literature shows that there are effective and relatively safe options for the treatment of childhood nocturnal enuresis. With regard to its effectiveness and conditional on proper use, preference should be given to desmopressin over the other available drugs. Satisfactory results can be expected with this drug; they are in fact better than those usually achieved with any other form of treatment. However, the therapy chosen in daily practice is frequently not appropriate for the type of enuresis/incontinence the patient has, which has led to standardisation of the definitions for childhood voiding disorders.[1]

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