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Alloussi S H[1], Mürtz G[2], Gitzhofer S[1], Eichel R[1], Lang C[1], Strugala G[2], Madersbacher H[3], Alloussi S[1]
1. *Neunkirchen Hospital, Department of Urology and Paediatric Urology, Neunkirchen, Germany,* ***2.*** *APOGEPHA Arzneimittel GmbH, Dresden, Germany,* ***3.*** *Neurourology Unit, University Hospital Innsbruck, Austria*

DESMOPRESSIN TREATMENT REGIMENS IN MONO- AND NONMONOSYMPTOMATIC ENURESIS: A REVIEW

Hypothesis / aims of study
The aim of this review was to evaluate the outcomes of studies in monosymptomatic and nonmonosymptomatic enuresis following different routes of application of desmopressin, monotherapy or combination therapies, and different structured withdrawal regimens.

Study design, materials and methods
Medline was searched for all studies performed in enuresis from 1982 - 2008, in which desmopressin was administered in different galenic formulations, alone or in combination with other treatment options. Studies were included, if children of at least 5 years of age (n = 93) had been investigated and if at least one of the following criteria was fulfilled:, treatment duration of at least 2 weeks (n = 93), reporting of long term (n = 39) or short term success rates (n = 93), reporting of adverse events (n = 76) and application of structured withdrawal program (n = 6). Definition of success was not conformative, we suggested as inclusion criteria a reduction in wet nights of more than 50 % (n = 93). In 29 studies monosymptomatic enuresis, in 71 studies nonmonosymptomatic enuresis was evaluated.
Minimally invasive diagnostic assessment prior treatment, including videocystourethrographie or urodynamics, was performed in 9 studies, most studies were restricted to a noninvasive diagnostic assessment.
The lack of nonconformative terminology especially in those studies conducted many years ago was minimized by applying ICCS terminology and state-of-the-art interpretation of methods and results of every single study.

Results
Altogether 93 studies were identified fulfilling the above mentioned inclusion criteria. Altogether 7083 patients were enrolled. 21 studies incorporated placebo either as mono- or combination-therapy. 65 studies administered desmopressin as monotherapy, 78 studies applied desmopressin intranasally, 23 studies applied desmopressin orally. In 38 studies desmopressin was combined with other treatment options, in particularly antimuscarinics (propiverine (n = 2), oxybutynin (n = 8)), enuresis alert (n = 24) or acupuncture (n = 4). Treatment periods varied from 2 weeks up to 24 months. Success criteria varied from subjective improvement to a range of clinically defined responses. Relapse rates were assessed in 29 studies, adverse events were evaluated in 76 studies.

Interpretation of results
1. Studies incorporating a minimally invasive diagnostic assessment (n = 9) achieved higher efficacy outcome rates compared to studies restricted to noninvasive assessment, at least in nonmonosymptomatic enuresis.
2. There were no significant differences in efficacy and tolerability with respect to the route of application of desmopressin.
3. There were no differences observed in adverse event rates and severity subject to dosage in the range of 10 - 80 mcg for the intranasal, in the range of 0.2 – 0.4 mg for the oral application.
4. Efficacy outcome rates in monosymptomatic enuresis treated with desmopressin are superior to outcome rates in nonmonosymptomatic enuresis.
5. Combination therapies achieved more favourable efficacy outcome rates compared to desmopressin monotherapy. However, the patient population, in which combination treatment instead of monotherapy is justified, still must be defined.
6. Combination therapy of desmopressin and antimuscarinics was more effective than desmopressin combined with enuresis alert. There seems to be a trend of superiority for propiverine compared to oxybutynin in these combination regimens, which needs to be confirmed in future studies.
7. Structured withdrawal programs for desmopressin show more favourable long term success rates than a sudden withdrawal of medication. Furthermore, relapse rates following structured withdrawal programs are significantly lower compared to those following sudden withdrawal.
8. Time-dependant (n = 5) and dose-dependant (n = 1) structured withdrawal programs can be differentiated. So far no superiority has been shown for either of these approaches, although evidence for final conclusions with respect to this issue is limited.

Concluding message
Most studies in this area of research incorporated only small case series, few placebo-controlled studies have been conducted so far, thus limiting the level of evidence.
Efficacy outcome rates of studies administering desmopressin in “enuresis” are dependent on the following issues: the disease itself (monosymptomatic or nonmonosymptomatic enuresis), monotherapeutic or combined therapeutic approaches, desmopressin withdrawal treatment regimens or sudden termination of medication.

References
Available from authors on request

Specify source of funding or grant	**No funding.**
Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**No**
This study did not require eithics committee approval because	**it is a study review.**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**