EURECA

Evidence-Based Management of Nocturnal Enuresis: An Overview of Systematic Reviews

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Nocturnal enuresis (bedwetting beyond the age of five years)(1) is fairly common in children; it reportedly affects almost 20% of five-year old children, and up to 2% of adolescents and young adults(2). Although a reliable population-based estimate in Indian children is not available, there is no reason to suspect that the burden is insignificant. A single cross-sectional, hospital-based study on sleep disorders reported 18.4% prevalence of nocturnal enuresis among 3-10y old children(3).

RELEVANCE

In the absence of organic disease, nocturnal enuresis can cause considerable emotional trauma, embarrassment, guilt, reduced quality of life, and stress- to the child and family. Failure of spontaneous resolution compounds the problem further.

The precise cause of nocturnal enuresis is unclear. The significance of this lack of clarity is that numerous interventions have been tried to control, treat, or cure it, with variable results. These include behavioural interventions, mechanical devices, pharmacotherapy, complex educational regimens and combinations of above. This necessitates a detailed evaluation of current evidence.

This overview of systematic reviews is designed to identify which interventions work, how they compare against each other and whether combination of interventions is beneficial. The specific question addressed is: In children with nocturnal enuresis(*population*), what is the impact of treatment with different modalities*(intervention, comparison)* in terms of control/cure(*outcome*)?

CURRENT BEST EVIDENCE

Literature search for Systematic Reviews using the term "*nocturnal enuresis*" was undertaken on 10 July 2010 in The Cochrane Library(Filter: *Record title*) and Medline(Limits: *Meta-analysis, randomized controlled trial, All child*). The Cochrane Library yielded 7 relevant Cochrane reviews, 1 other systematic review and 188 methodologically appraised clinical trials. Medline yielded 96 citations but no additional new systematic reviews. Eight systematic reviews are published till date(4-11). Searching for randomized controlled trials beyond the search dates in the respective systematic reviews yielded 16 potentially relevant citations, of which 7 were relevant(12-18). However, none of these had data that could be combined with the data in the systematic reviews.

Seven(4-10) of the eight reviews were authored by one group of Cochrane reviewers; hence had uniform outcome measurements and high methodological quality. The eighth review(11) evaluated acupuncture, but owing to methodological limitations is not considered in this Overview. Outcomes were reported as symptom relief (defined as mean reduction in number of wet nights per week), treatment failure (relative risk of failure to remain dry for 14 consecutive nights during treatment), relapse during treatment (relative risk of failure to remain dry after achieving 14 consecutive dry nights) and persistence/recurrence of symptoms (mean difference in number of wet nights after cessation of treatment). None of the reviews described adverse effects of therapy, quality of life and cost as outcomes.

As the objective of this Overview was to identify the most efficacious intervention(s), data from the reviews were extracted in the following order: (*i*) intervention versus no treatment or placebo to identify efficacious interventions, (*ii*) efficacious interventions of one type versus similar interventions, (*iii*) efficacious interventions of one type versus efficacious interventions of another type, and (*iv*) combinations of interventions versus other interventions, singly or in combination. **Table I-IV** (available as supplementary tables on *www.indianpediatrics.net*) summarize the data.

The Overview revealed that the following interventions are efficacious: (*i*) simple behavioural interventions including retention control training and cognitive/counselling therapy(4), (*ii*) alarms(6), (*iii*) desmopressin(7), (*iv*) tricyclic antidepressants (imipramine, desipramine, viloxazine, amitriptyline)(8), and (v) other drugs *viz* indomethacin, diclofenac, diazepam, and atomoxetine(9). Desmo-pressin is efficacious in doses as low as 10mg/d; higher doses do not appear to give greater benefit(7). The oral and nasal routes appear to have comparable efficacy(7). No specific type/ mechanism of alarm appears to be superior(6). Waking the child up(4), complex dry bed training(5), and play with supportive therapy(10) do not appear to be superior to placebo/nothing. Other tricyclics and drugs not listed above are also not efficacious(8,9).

Comparison of similar interventions revealed that desmopressin is superior to indomethacin and diclofenac(7), but similar to amitriptyline or imipramine(8). Imipramine has similar efficacy to viloxazine or clomipramine(8). Retention control training is as efficacious as the more complex dry bed training(5).

Alarms are superior to retention control training(4), waking(4), dry bed training(5), and cognitive/psychological/counselling therapy(10). Their effect appears comparable to combination of star chart with rewards(4). It is difficult to establish whether alarms are superior (or inferior) to desmopressin or imipramine(6). There is no added efficacy when alarms are augmented with retention control training(6), dry bed training(6), or desmopressin(7). Desmopressin therapy is superior to retention control training(4), and psychological counselling(10). There is no benefit of augmenting desmopressin with alarm, amitriptyline or oxybutinin(7). Amitriptyline is superior to behavioural interventions(8). Limited data suggests that acupuncture is superior to star chart(10). Combinations of start chart with rewards or lifting(4), imipramine and oxybutinin(8) combination may be superior to monotherapy. However, no other combinations are particularly efficacious. Fluid restriction and avoidance of punishment could be useful(5). Data were also utilized from the additional RCTs(12-18).

CRITICAL APPRAISAL

The complexity of the clinico-social condition and its consequences for the child and family, raise the following pertinent issues to determine the most suitable approach in the local context.

Is the significance of nocturnal enuresis in Indian children similar to developed countries? It is reported that majority of Indian children co-sleep with parents(3), often till early adolescence, despite the availability of separate rooms/beds. This fact, coupled with differences in sleep hygiene, make the relatively benign condition disturbing for the whole family, rather than individual child alone. Besides, the logistics of arranging multiple sets of bedclothes, linen, etc and manually washing/cleaning them, could be more complex in our setting.

Should nocturnal enuresis be treated? A number of children are likely to recover/improve over time. The declining prevalence till the mid-teens suggests an annual spontaneous resolution rate of at least 10-15% among affected children. Unfortunately, it is not possible to predict this for an individual child. Therefore, decision to intervene(or otherwise) has to be guided by age of the child, assessment of the distress to the child/ family, and practical issues in applying one or more interventions.

Can interventions efficacious in developed countries be applied here? The initial approach to managing nocturnal enuresis (conservative steps, avoiding punishment, managing fluid intake/output appropriately, simple behavioural interventions) can be practised with adequate child and family

EURECA CONCLUSION IN THE INDIAN CONTEXT

- Alarms, desmopressin and some tricyclic antidepressants are efficacious to manage nocturnal enuresis.
- Some simple behavioural interventions (managing fluid intake, avoiding punishment, retention control training and motivation by rewards or star charts) are also beneficial.
- There is limited data to support complex behavioral interventions, and combinations of treatment modalities.
- Treatment plans should be individualized based on the specific situation of an individual child and family.

motivation, patience and understanding. More complex (and possibly expensive) therapies including alarms, pharmacotherapy, and combinations, require individualized decisions.

Do we need more research? Barring desmopressin, alarms and some tricyclic drugs, data is limited for most other interventions in terms of quantity and/or quality. Further, some of the older trials do not have the modern methodological refinements to reduce bias. It would be appropriate for our setting to evaluate not only the efficacy of behavioural, device and pharmacological interventions, but also their effectiveness in terms of logistics, cost, compliance, follow-up, social support, etc. This would necessitate health technology assessment research, rather than more individual trials.

EXTENDIBILITY

There is paucity of research data from developing countries, and almost none from India. In addition, for the reasons cited above, it may not be possible to directly extrapolate research data on efficacy and expect similar effectiveness. An appropriate evidence-based management solution would be to discuss the efficacious options and factor-in the opinions, perceptions and convenience of the child/family (patient values) and individualize treatment plans.

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REFERENCES

1. WHO. Nonorganic enuresis. The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines. Geneva: WHO, 1992.
2. Feehan M, McGee R, Stanton W, Silva PA. A 6 year follow-up of childhood enuresis: prevalence in adolescence and consequences for mental health. J Paed Child Health 1990; 26: 75-79.
3. Bharti B, Malhi P, Kashyap S. Patterns and Problems of Sleep in School Going Children. Indian Pediatr 2006; 43: 35-38.
4. Glazener CMA, Evans JHC. Simple behavioural and physical interventions for nocturnal enuresis in children. Cochrane Database Syst Rev 2004; 2: CD003637.
5. Glazener CMA, Evans JHC, Cheuk DKL. Complementary and miscellaneous interventions for nocturnal enuresis in children. Cochrane Database Syst Rev 2005; 2: CD005230.
6. Glazener CMA, Evans JHC, Peto RE. Alarm interventions for nocturnal enuresis in children. Cochrane Database Syst Rev 2005; 2: CD002911.
7. Glazener CMA, Evans JHC. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev 2002; 3: CD002112.
8. Glazener CMA, Evans JHC, Peto RE. Tricyclic and related drugs for nocturnal enuresis in children. Cochrane Database Syst Rev 2003; 3: CD002117.
9. Glazener CMA, Evans JHC, Peto RE. Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics). Cochrane Database Syst Rev 2003; 4: CD002238.
10. Glazener CMA, Evans JHC, Peto RE. Complex behavioural and educational interventions for nocturnal enuresis in children. Cochrane Database Syst Rev 2004; 1: CD004668.
11. Bower WF, Diao M, Tang JL, Yeung CK. Acupuncture for nocturnal enuresis in children: a systematic review and exploration of rationale. Neurourol Urodyn 2005; 24: 267-272

12. Chen YJ, Zhou GY, Jin JH. Transcutaneous electrical acupoint stimulation combined with auricular acupoint sticking for treatment of primary nocturnal enuresis. Zhongguo Zhen Jiu 2010; 30: 371-374 (abstract only).

13. Vogt M, Lehnert T, Till H, Rolle U. Evaluation of different modes of combined therapy in children with monosymptomatic nocturnal enuresis. BJU Int 2010; 105: 1456-1459.

14. Van Kampen M, Lemkens H, Deschamps A, Bogaert G, Geraerts I. Influence of pelvic floor muscle exercises on full spectrum therapy for nocturnal enuresis. J Urol 2009; 182 (4 Suppl): 2067-2071.

15. Gelotte CK, Prior MJ, Gu J. A randomized, placebo-controlled, exploratory trial of Ibuprofen and pseudoephedrine in the treatment of primary nocturnal enuresis in children. Clin Pediatr (Phila) 2009; 48: 410-419.

16. Ma J, Zhang YW, Wu H, Jiang F, Jin XM. A randomized controlled clinical trial for treatment of children with primary nocturnal enuresis. Zhonghua Er Ke Za Zhi 2007; 45: 167-171.

17. Ferrara P, Marrone G, Emmanuele V, Nicoletti A, Mastrangelo A, Tiberi E, et al. Homotoxicological remedies versus desmopressin versus placebo in the treatment of enuresis: a randomised, double-blind, controlled trial. Pediatr Nephrol 2008; 23: 269-274.

18. Sumner CR, Schuh KJ, Sutton VK, Lipetz R, Kelsey DK. Placebo-controlled study of the effects of atomoxetine on bladder control in children with nocturnal enuresis. J Child Adolesc Psychopharmacol 2006; 16: 699-711.