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A Systematic Review of Interventions of the Effectiveness of Interventions for Managing Childhood Nocturnal Enuresis

CRD REPORT 11

A SYSTEMATIC REVIEW OF THE EFFECTIVENESS OF INTERVENTIONS FOR MANAGING CHILDHOOD NOCTURNAL ENURESIS

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PREFACE

By 1995 the NHS Centre for Reviews and Dissemination (NHS CRD) had undertaken reviews on many medical topics, providing important benchmarks for professional practice, but the topic of childhood enuresis had not yet been tackled. In April 1995 the national charity ERIC - the Enuresis Resource and Information Centre, approached the NHS CRD and the idea was born to undertake a Review that compared the effectiveness of the various treatments for nocturnal enuresis. It became a reality through a successful application by the NHS CRD to the Department of Health Research and Development Programme.

In addition to its advice and information-giving role, a major aim of ERIC is to identify areas in which research is needed, to define research questions and to act as a consultancy body for those undertaking new research. We saw a comprehensive enuresis review as an important baseline for these activities.

The guiding force behind ERIC's research-related activities is the National Enuresis Research Steering Group, a national panel of experts in the field, currently chaired by Dr Jonathan Evans, consultant paediatric nephrologist Nottingham NHS Trust. Set up eight years ago, this group initiated the first working definitions on treatment outcome (1) and the first guidelines on minimum standards of practice in the treatment of enuresis (2). Its members, together with many other health professionals in the field, were pleased to comment upon working drafts of the NHS CRD Review on enuresis.

ERIC is indebted to the NHS CRD and in particular to Dr Lister-Sharp for undertaking such a rigorous and thorough review. Its outcome will influence ERIC's future publications and it will, I believe, provide a sound benchmark for health professionals when tailoring treatment programmes to the needs of the individual children with enuresis and their families.

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1 Butler RJ. Establishment of working definitions in nocturnal enuresis. *Archives of Disease in Childhood* 1991; 66: 267-271.

2 Morgan R. *Guidelines on Minimum Standards of Practice.* 1993, revised 1996, Enuresis Resource and Information Centre.

EXECUTIVE SUMMARY

Research Questions

This review sought to assess and compare the effectiveness of interventions for treating bedwetting (nocturnal enuresis).

Interventions

Behavioural (e.g. enuresis alarms); pharmacological and complementary approaches are considered.

Outcome measures

The outcomes considered in the review are numbers of participants attaining 14 consecutive dry nights (initial success); change in the mean number of wet nights per week during treatment; number of initial successes relapsing and mean number of wet nights per week when participants were followed up after treatment had ceased.

Participants

People suffering from nocturnal enuresis which could not be attributed to organic causes. The majority of identified studies included children.

Literature search

The following electronic databases were searched: AMED; ASSIA; BIDS; BIOSIS Previews; CINAHL; DHSS Data; EMBASE; MEDLINE; PsycLIT and SIGLE. In addition, organisations, manufacturers, researchers and health professionals concerned with enuresis were contacted for information. The reference sections of obtained studies were also checked for further trials.

Inclusion criteria

Only randomised controlled trials (RCTs) which excluded participants with organic causes for their bed wetting and systematically measured baseline levels of bed wetting were included in the review. Studies concerned solely with daytime wetting were not included.

Studies included in the review

Sixty two RCTs are included. These evaluate the effectiveness of desmopressin (18 trials); imipramine (19); other drugs (13); enuresis alarms (16); Dry Bed Training (8); combined behavioural and drug approaches (2); retention control training (3); wakening (1) and complementary approaches (2). No RCTs meeting the inclusion criteria were found which evaluated the effectiveness of star charts and rewards; fluid deprivation; lifting; psychotherapy or surgery. A number of trials compared several interventions.

Data synthesis

The large number of RCTs evaluating some interventions permitted statistical pooling of results in order to obtain a more precise estimate of overall effect of an intervention. The results are presented in terms of random effects weighted mean differences (WMD), giving the difference in mean number of wet nights per week, relative risks (RR) and 95% confidence intervals (CI). The review also presents tables of individual study details and a narrative discussion of the results.

Sensitivity analysis

Three sensitivity analyses were undertaken to assess the effects of relaxing the following inclusion criteria on the results.

a) studies which otherwise met the inclusion criteria but were not randomised controlled trials;
b) randomised controlled trials without systematic measurement of baseline levels of wetting;
c) randomised controlled trials where organic causes of wetting had not been excluded.

KEY FINDINGS

Desmopressin

Desmopressin is effective in reducing bed wetting in a variety of doses and forms. Patients treated with 10 µg desmopressin have, on average, two fewer wet nights per week than those treated with placebo: WMD: -2.19 (95% CI: -3.72 to -0.65). In addition, participants treated with desmopressin were 4.5 times more likely to attain 14 consecutive dry nights than those treated with placebo: RR 4.5 (1.4, 15.0). However this effect does not appear to be sustained after treatment has finished. No difference was found between desmopressin and placebo in the number of wet nights per week at post treatment follow up; WMD (10 µg desmopressin): 0.13 (-1.1 to 1.34). These results are supported by the sensitivity analysis.

Imipramine

Imipramine is also effective in reducing bed wetting. Participants treated with imipramine had, on average, 1.3 fewer wet nights per week than those given placebo: WMD = -1.27 (95% CI -

1.83 to -0.72). In addition people treated with imipramine were 4 times more likely to attain fourteen consecutive dry nights than those receiving placebo: RR = 4.2 (95% CI: 1.2 to 15.0). There is no conclusive evidence about the long term effectiveness of imipramine. These findings are supported by all three sensitivity analyses, the effectiveness of imipramine being demonstrated across a variety of client groups and study designs

Imipramine and desmopressin have been compared in only one randomised controlled trial - they were found to be equally effective.

Other drugs

Desipramine was 3.5 times more likely than placebo to result in 14 consecutive dry nights (95% CI: 1.1, 11.8).

Desipramine was also found superior to imipramine in a randomised controlled trial which had failed to adequately exclude organic causes of enuresis and to be comparable in effectiveness to imipramine in a non-randomised controlled trial which otherwise met the inclusion criteria.

There is no reliable evidence from included randomised controlled trials to suggest that any other drug is more effective than placebo.

Star charts and rewards

No randomised controlled trials meeting the inclusion criteria of this review investigated the effectiveness of star charts and rewards. However, a non-randomised controlled trial which otherwise met the inclusion criteria reported that a token economy system produced significantly fewer wet nights than control. A randomised controlled trial without a systematic baseline measurement of wetting found that waking and the use of a star chart was initially more effective than amitriptyline.

Enuresis alarms

Participants receiving alarm treatment were thirteen times more likely to achieve fourteen consecutive dry nights than the control group: RR: 13.3 (95%CI: 5.6 to 31.5).

Inclusion of non-randomised studies decreased the estimate of benefit, but alarm treatment was still highly effective: RR: 9.7 (95%CI: 4.7, 19.9).

There is no evidence to suggest that any one type of alarm is superior to another. However, most comparisons have involved single small trials which may not have had adequate power to demonstrate any differences.

Supplementation of the alarm by retention control training does not appear to improve its effectiveness. Supervision of alarm treatment did not improve its effectiveness but again, this comparison was based on a single small trial. However, participants who received alarm treatment alone were three times more likely to relapse than those who received alarm treatment augmented by an over-learning schedule: RR = 3 (95% CI: 1.04 to 8.6).

The included trials reported relapse rates for alarms ranging from about 30 to 70% at 3 months.

Multidimensional Behavioural Treatment Programmes

Participants receiving Dry Bed Training (DBT) (including an alarm) were 10 times more likely to attain 14 consecutive dry nights than the control group (95% CI: 2.7, 37.2) regardless of the specific training situation.

DBT and alarm treatment were equally likely to result in 14 consecutive dry nights: RR: 1.1 (95% CI: 0.7 to 1.8). Participants given DBT and those given alarm treatment were equally likely to relapse RR: 1.00 (95% CI: 0.7 to 1.5).

The presence of an alarm seems to be the only essential part of DBT - participants receiving DBT without an alarm were no more likely than the control group to attain 14 consecutive dry nights RR: 2.5 (0.55, 11.4). Participants given DBT using an alarm were 4 times more likely to attain 14 consecutive dry nights than those not using an alarm RR = 4.1 (95% CI: 2.2 to 7.9).

At three months relapse rates for DBT ranged from 10 to 100% - the latter being DBT without an alarm

The sensitivity analysis allowed an additional multi dimensional behavioural intervention to be considered - Full Spectrum Home Training - a package involving use of an enuresis alarm, retention control training and over learning. A series of randomised controlled trials which had not excluded organic causes of wetting found that although initially results of Full Spectrum Home training were no different to alarm treatment, there were fewer relapses in this group.

Comparing drugs and alarms

Although desmopressin was initially superior to alarm in reducing the number of wet nights per week WMD = -1.7 (95% CI: -0.45, -2.96); after 3 months of treatment patients using the

alarm had 1.4 fewer wet nights per week than desmopressin WMD = -1.4 (95% CI: -2.65, -0.15).

Participants receiving the alarm intervention were also 9 times less likely to relapse than those given desmopressin: RR = 9.1 (95% CI: 1.3, 50).

Psychotherapy

No randomised controlled trials meeting the inclusion criteria assessed the effectiveness of psychotherapy. However, one non-randomised study which otherwise met the inclusion criteria found no significant difference in the attainment of 14 consecutive wet nights or relapsing between psychotherapy and control.

Combined psychological and pharmacological approaches

Combining alarm and drug therapy was found to be superior to alarm treatment alone. The addition of desmopressin to an alarm schedule resulted in 1 less wet night per week WMD: -1.0 (95% CI: -1.6, -0.6). Similar results were found in a quota allocation study which otherwise met the inclusion criteria.

Retention Control Training

There was no evidence from randomised controlled trials meeting the inclusion criteria to suggest that retention control training either alone or as an adjunct to alarm treatment was effective in the treatment of bed wetting.

Wakening

There is slight evidence from randomised controlled trials meeting the inclusion criteria that random awakening results in fewer wet nights per week than treatment with placebo.

No randomised controlled trials meeting the inclusion criteria of this review investigated the effectiveness of surgery, fluid deprivation or the effectiveness of lifting.

Complementary treatments

There was no reliable evidence from randomised controlled trials meeting the inclusion criteria to suggest that either hypnosis or chiropractic treatment were superior to control.

Implications

A variety of behavioural and pharmacological interventions have been shown to be effective in the management of nocturnal enuresis in both domestic and residential settings.

Use of enuresis alarms can help children to attain at least fourteen consecutive dry nights. However, because it can take up to sixteen weeks to attain dryness families can become discouraged sometimes resulting in poor compliance. Children treated with alarms frequently resume wetting the bed but relapse rates can be reduced by the incorporation of over-learning procedures. Multidimensional behavioural treatment programmes such as Dry Bed Training have not been shown to be more effective than alarm treatment.

Two drugs, desmopressin and imipramine rapidly reduce the number of wet nights per week. However, there is no reliable information about the longer term effectiveness of these drugs. Patients and their families need to be warned of their potentially lethal adverse effects and counselled how to avoid them. The only direct comparison of the two drugs does not indicate any difference in their clinical effectiveness, a finding reinforced by other available studies. However, treatment by desmopressin is considerably more expensive than imipramine. Therefore, until further direct comparisons between these drugs are undertaken, imipramine, if carefully used, would appear to be the more cost effective option and should be the drug of choice if pharmacological approaches are to be used.

The rapidity of response of drug treatments is not evidence of their overall superiority over enuresis alarms. In the only useful direct comparison between drugs and alarms, whilst desmopressin had the most immediate effect, alarm treatment showed a more sustained benefit. In the long term, alarm treatment would appear to be the most clinically effective and because the costs of drug therapy are recurring, also the more cost effective intervention. However, in day to day clinical practice and in the absence of definitive research evidence the full range of options should be discussed with children and their families.

No studies meeting the full inclusion criteria were located which investigated the effectiveness of star charts and rewards, fluid deprivation or lifting - all of which are commonly used interventions. It is important to evaluate their effectiveness. In addition the review has identified some other treatments that are worthy of further research - desipramine, diclofenac sodium, viloxazine and hypnosis.

Much of the research into the management of enuresis is of poor quality and direct comparisons are few. Studies need to use samples of sufficient size to be able to detect

clinically important differences. It would be useful if treatment outcomes were reported both in terms of numbers achieving fourteen consecutive dry nights and also changes in the numbers of wet nights per week. More representative groups of children should be studied and further research is required into which interventions are appropriate in different circumstances.

1 INTRODUCTION

This systematic review of the effectiveness of treatment for nocturnal enuresis has been undertaken by the NHS Centre for Reviews and Dissemination, University of York, in response to a request from the Enuresis Resource and Information Centre (ERIC) - a consumer group concerned to raise public awareness of bed wetting. Funding for this work was obtained from the Department of Health's Research and Development programme.

1.1 Definition of Enuresis

Bed wetting is a complaint that affects many families. According to the ICD-10 Classification of Mental and Behavioural Disorders, if regular bed -wetting continues beyond the age at which dryness is usually attained and cannot be attributed to neurological disorders, epileptic attacks or structural abnormality of the urinary tract, then an individual is said to suffer from non-organic enuresis (F98.0, (2)). The associated diagnostic guidelines state " ... enuresis would not normally be diagnosed in a child under the age of five years or with a mental age under four years." The Diagnostic and Statistical Manual gives the additional diagnostic criteria that there should be "at least two such (wetting) events per month for children between ages of five and six, and at least one event per month for older children" (3).

When children have never experienced a significant period of dry nights, the enuresis may be classified as primary or persistent; if bed wetting has resumed after a period of at least twelve dry months in a child over the age of three, the enuresis is said to be secondary or acquired (4).

This review will focus on nocturnal enuresis. Although day time wetting is a significant problem and is often associated with bed wetting, nocturnal and diurnal enuresis are usually considered separately. The absence of organic cause is less clear cut for daytime wetting; more structural abnormalities and functional disorders of the urinary tract were found in daytime wetters than controls (5). A study of 3556 seven-year-old Swedish school entrants found that 3% of girls and 2% of boys wet themselves during the day at least once a week (6). Most of these children also had urgency suggesting that daytime wetting is of detrusor origin, caused by unstable bladder contractions. Bacteriuria was also a common finding in the daytime wetting girls (6). It has been suggested that there are at least two groups of children who wet the bed (7)- those who only wet at night and those who wet both during the day and at night with different aetiologies underlying the two conditions. If daytime symptoms are present, investigations to identify physical causes such as urinary tract dysfunction, congenital malformation and neurogenic disorders are usually necessary (8).

1.2 Prevalence

The prevalence of nocturnal enuresis is difficult to establish. Reviews of the epidemiology of bed wetting have commented that comparisons of results of studies are hindered both by methods of investigation and variation in how enuresis is defined (9, 10).

A review of international literature concluded that the prevalence of bed wetting decreases with increasing age (9). Overall the prevalence decreases by 14 to 16% per year in children aged five to nineteen years (11). Bed wetting is less common among girls than boys and the decline in prevalence with age seems to occur earlier in girls than boys (9, 12). At age six years, the male to female ratio of enuresis is three to two (11). These sex differences have led to a call for changes in the DSM-III definitions, with the defining age for enuresis in boys being raised to eight years (12).

In the United Kingdom, the generally quoted prevalence rates are that 15 to 20% of five year olds, 7% of seven year olds, 5% of ten year olds, 2 to 3% of twelve to fourteen year olds and 1 to 2% of those aged fifteen and over wet the bed twice a week on average (4). These are based on a behavioural questionnaire sent to parents of all children in a given age group attending local authority schools in the Isle of Wight (13). The incidence of nocturnal enuresis is particularly high amongst children in residential care (14).

There is a pilot study underway to investigate prevalence of nocturnal enuresis among the homeless (15). The prevalence is difficult to estimate because those who report enuresis also tend to report a consumption of alcohol. Thus there may be vulnerability but the rate of enuresis is difficult to gauge.

A long term follow up of 1129 children who had attended an Enuresis Clinic but who had not received alarm treatment found an average spontaneous cure rate of 14% for children between the ages of five and nine years, 16% for those aged ten to fourteen years and 16% for the fifteen to nineteen year olds. Three per cent of the patients were still wetting at 20 years of age (16).

1.3 Socioeconomic Factors

It is often stated that there is a link between bed wetting and socioeconomic factors but the evidence is equivocal. In a cohort study of 12,000 children, about whom educational, social and medical information was gathered at age 5, 7 and 11, the National Child Development Survey found that children in social classes IV and V (unskilled and semi-skilled) and also those subject to other environmental factors such as over-crowding were more prone to wet

the bed at age 11 and to a lesser extent at ages of five and eleven (17). However, the Isle of Wight study only found a weak and inconsistent relationship between enuresis and parental occupation at age 9 to 10 and no association at age 14 (13). These "class" differences were only significant in girls. When parents of 1,806 Irish school children were surveyed the association between enuresis and social class followed a J-shaped curve, the lowest incidence of enuresis found in class IV (18). Fathers of children with enuresis were more likely to be unemployed (19%) than fathers of controls (12%) but mother's employment status was not associated with enuresis. No relationships between place of residence, adverse housing or family size and bed wetting were found.

1.4 Aetiology

The aetiology of enuresis is unclear; a variety of potential explanations are discussed below.

1.4.1 Genetics

Twin studies and investigations of family incidence of enuresis suggest a genetic component (19). A significantly higher percentage of identical twins (monozygotic) than non-identical twins (dizygotic) were both found to suffer from enuresis (68 per cent as compared with 36 per cent). Enuresis was also found to occur with high frequency among parents, siblings and other close relatives of bed wetters (20). Seventy-five per cent of all children with functional enuresis have a first degree biological relative who has or has had the disorder (3). Linkage analyses of one large three-generation family and four smaller two or three-generation families has indicated that an "enuresis gene" may be located on chromosome 13q. (21).

1.4.2 Bladder Capacity and Function

Unlike children exhibiting daytime wetting, those with monosymptomatic bed wetting have normal bladder capacity and there is no conclusive evidence to implicate bladder instability (8). Bedwetting is most likely to occur when the bladder is filled to the equivalent of its maximum functional daytime capacity (22). However, many people with enuresis do not exhibit the usual circadian rhythm in urine output and the normal nocturnal increase in the antidiuretic hormone arginine vasopressin (AVP) is frequently absent among bed wetters (8). However, this does not explain why people with enuresis do not wake up and go to empty their bladders in a toilet.

1.4.3 Sleep Levels and Arousability

Wetting incidents are not especially linked to any particular sleep stage and can occur during deep and light sleep. However, the frequency of wetting in a given sleep stage is related to the amount of time spent in that stage (23). Studies carried out at the University of Aarhus found that children who wet the bed had sleep patterns comparable to those of normal children and were able to void during any sleep stage (22).

Although anecdotes suggesting that children who wet the bed are harder to wake abound, there is no conclusive evidence that these children are more difficult to waken. In addition it is not clear how difficult it is to wake children who do not wet the bed - parents rarely have cause to wake them in the middle of the night. The issue of arousability is complex, as it is not a question of depth of sleep but rather moving between sleep levels.

1.4.4 Maturational Delay

Bed wetting has been attributed to maturational delay (7). This could account for the spontaneous remission rate associated with nocturnal enuresis.

A dual developmental delay in the central nervous system has been suggested, consisting of a failure to recognise and respond to a full bladder and also failure to suppress the micturition arc during sleep (24). Koff hypothesises that both elements are necessary in an explanation of the aetiology of enuresis but neither on its own is sufficient.

1.4.5 Learned Response

Behavioural interventions are based on the idea that the ability to stay dry at night is a learned response; nocturnal enuresis being attributed to habit deficiencies, poor learning experiences and the lack of appropriate reinforcement contingencies (25). A sensitive period for the emergence of bladder control around the third year of life has been hypothesised along with a vulnerable period in which stresses may interfere with the ability to remain dry at night (26).

1.4.6 Bio-behavioural Approach

These elements have been combined into a bio-behavioural approach. This suggests " that changes in behaviour brought about by application of learning and conditioning principles may affect the physiological mechanisms that cause and maintain the problem." (p141) (27). In other words, the underlying pathophysiology of enuresis can be altered using behavioural techniques, if not, behavioural techniques would not influence wetting.

1.4.7 Psychological, Emotional and Behavioural Difficulties

Psychiatric and psychological disorders may be associated with enuresis but the causality is unclear (28). An association between enuresis and emotional disturbance was found in girls but not boys in the Isle of Wight survey (13); there was also an increased risk of daytime wetting. The survey of nearly 2,000 Irish school children also found a strong association between enuresis and behavioural disorders (18). Children who wet the bed were also more likely to have a history of stressful events in childhood (18). After reviewing the psychological implications of treatment and non-treatment of enuresis it was concluded that enuresis is associated with behavioural abnormalities but that most children with enuresis are not psychiatrically disturbed (29).

1.4.8 Other

Other factors which may contribute to bed wetting include constipation and sleep apnoea. However, the evidence is sketchy (30).

Constipation may interfere with cortical perception of normal bladder sensory information and additionally the sufferer may be preoccupied with control of the anal sphincter causing contraction of the bladder sphincter (30).

Some children start wetting the bed with the onset of upper airway obstructive symptoms such as obligate mouth breathing and snoring. There was a 7% reduction in wet nights among such children after operations to provide more functional upper airway (reported in(30)).

Diet and mild caffeine drinks with diuretic effects (e.g. Cola) have been implicated (4).

1.4.9 Primary and Secondary Enuresis

In general it is assumed that physiological factors are of significance in primary enuresis, whereas psychological factors are of importance in secondary enuresis (31). There is no evidence to suggest that the converse is true. Approximately 80% of nocturnal enuresis is primary and 20% secondary (32). Difficulties of definition of primary and secondary enuresis may arise because of unreliability on the part of parents in specifying periods of dryness.

1.5 Services for Children with Enuresis

Although bed wetting in itself is pathologically benign and has a high rate of spontaneous remission, it may bring social and emotional stigma, stresses and inconvenience to both the person with enuresis and their families (33). Children who wet the bed may experience parental disapproval, sibling teasing and repeated treatment failure which may lower self esteem (34). The children may also be at increased risk of emotional and physical abuse (34).

Consequently it is important that enuresis is properly managed on "humane grounds" (35). The appropriateness of professional intervention depends on individual circumstances: if there is a family history of enuresis, bed wetting may be better accepted (32). Butler suggests that bed-wetting becomes a problem when parental concern is expressed - this, unlike the formal definitions, is not dependent on age (36).

Primary care for people who wet the bed is often carried out by general practitioners and much is now being done by practice nurses. Moreover, school nurses are becoming more organised in their delivery of service. Questions relating to bed wetting may be included in structured assessments or children may be referred by the general practitioner or teacher. Bed wetting may be discovered when a child is seen for a complaint other than enuresis, with the bed wetting disclosed as a result of questioning.

It is likely that different health professionals work with different patient populations. However, professional background may not be as important as the interest and enthusiasm of the person providing the care (37).

The Enuresis Resource and Information Centre has produced "A guide to enuresis: A guide to treatment for professionals" (4). This details management options for children who wet the bed. Having established that the child is at least five years old (ie at an age where one could reasonably expect a dry bed (37)) and wants to become dry (38), the practitioner should thoroughly assess the situation, including a general physical examination, urinalysis and investigation of attitudes; information and reassurance should be given and an appropriate treatment selected (4). A period of observation is critical as it may be found that the sufferer, in fact only wets the bed infrequently, or may stop altogether (28, 30).

The Enuresis Information and Resource Centre has also produced guidelines on minimum standards of practice in the treatment of enuresis to assist managers and practitioners in the planning, execution and evaluation of enuresis services (39).

1.6 Interventions

Pharmacological, psychological and a variety of "unconventional" interventions have been used with people who wet the bed. The main interventions are briefly summarised below.

1.7 Pharmacological

Three organ systems have been targeted, based on theoretical grounds, for pharmacological interventions: the kidney and diuresis; the central nervous system (and sleep) and the urinary bladder and sphincter function (40).

1.7.1 Desmopressin

Desmopressin is an analogue to the natural human pituitary hormone arginine vasopressin. The antidiuretic effect results from an increased reabsorption of water from the kidney leading to a reduced volume of, more concentrated, urine entering the bladder (40). In 1972, desmopressin was introduced in a dropper bottle allowing drops to be placed into the nose. It has also become available as a measured dose spray giving doses of multiples of 10 μg; a single dose pipette giving doses in multiples of 20 μg and 0.2 mg oral tablets. In general 20 to 40 μg is given intra nasally at bed-time independent of age and body weight (41). Although initially prescribed for short term treatment, longer term treatment of a least a year may be considered appropriate for some children. Treatment should be withdrawn for at least one week for reassessment after 3 months (42).

About 10% of a dose of desmopressin is absorbed from the nasal mucosa after intra-nasal administration, the plasma concentration of desmopressin reaching a maximum after about 40 to 55 minutes after administration. The biological effect of desmopressin lasts for 10 to 12 hours (41).

A review of the adverse effects of desmopressin used to combat nocturnal enuresis (43) noted that 22 adverse experiences, most commonly nasal irritation and nose bleeds, have been reported in 7 published studies. Twelve additional published studies reported no adverse events. Although noting that 21 cases of water intoxication have been spontaneously reported by physicians and patients up to 1992, the authors of the review concluded that desmopressin seems to elicit few and mostly non-serious adverse events in children treated for nocturnal enuresis (43). Water intoxication is a serious condition, the symptoms of which include headache, nausea, hyponatraemia, cerebral oedema and convulsions. A systematic review of studies reported data on the serum sodium during treatment with desmopressin and case reports of seizures or altered levels of consciousness (44). The authors concluded that mild asymptomatic hyponatraemia might develop in 1% to 10% of patients treated with desmopressin for nocturnal enuresis. The authors recommend that desmopressin should only be prescribed with specific instructions regarding the risks associated with excess ingestion of fluid - patients should be counselled not to ingest more than 240ml (8oz) fluid on any night that desmopressin is given.

1.7.2 Imipramine

Imipramine is a tricyclic antidepressant acting on the central nervous system. Additionally, it has anticholinergic and/or anti-spasmodic effects and local anaesthetic properties and also affects the sleep centre and adrenergic neurotransmitter re-uptake blockade (45). The data sheet for imipramine gives age/weight related dosages ranging from 25 mg for 6 year olds (weight 20 to 25 kg) to 50- 75 mg for those over 11 years of age. It is clearly stated that imipramine is not to be given to children under 6 years of age and the dose should not exceed 75 mg daily. The maximum period of treatment should not exceed three months (including gradual withdrawal) and a full physical examination should be given before a further course is prescribed (46).

Minor side effects include constipation, difficulty in initiating micturition, irritability, insomnia, dry mouth, nausea, drowsiness, reduced appetite and rarely, adverse personality changes (47). Poisoning due to over dose is a major concern (33). This can result in cardiac arrhythmias, conduction blocks, hypertension, respiratory arrest, convulsions and coma (47). Both the recipient of a prescription of imipramine and siblings are potentially at risk from accidental poisoning (48).

1.7.3 Other Drug Interventions

Other tricyclic antidepressants used include desipramine, amitriptyline and nortriptyline. These have the same associated risks as imipramine. Historically, amphetamine and diazepam and more recently oxybutynin have also been used.

1.8 Psychological

Psychological interventions assume that the ability to remain dry at night is a learned response which can be achieved using conditioning techniques if it has not arisen spontaneously.

1.8.1 Star Charts And Reward Systems

Star charts and reward systems are behavioural interventions which use positive reinforcement to encourage a desired behaviour. The child is rewarded for attaining an achievable goal, such as remaining dry all night - or if this is too ambitious, an intermediate goal such as getting up to go to the toilet. These schemes should be negotiated with the child and family and if properly used positively reinforce dry nights and can help reduce the negative emphasis on wet beds. These are often the first type of treatments proposed (49). However, unless used with care, a child may feel a failure if the reward is not attained (4).

1.8.2 Enuresis Alarms

Enuresis alarms consist of some kind of alarm which is activated by inappropriate micturition. The first enuresis alarms were bed-based, the child sleeping on a pad or mat containing an electrical circuit. Urine, coming into contact with this would complete the circuit causing a bell to ring. The alarm is intended to change the meaning of the sensation of having a full bladder from a signal to urinate to a signal to inhibit urination and waken (50). There are now many variations: the alarm may be a bell, buzzer, visual signal such as a light or may vibrate. There are also many different tones and intensities. In "mini-alarm" systems, the sensor is located placed in pants, producing a discrete, portable system.

However, it remains unclear how the psychological effects of conditioning treatment affect physical functioning. Is successful treatment accompanied by changes in bladder functioning and in depth of sleep?

1.8.3 Over Learning

An over-learning procedure may be initiated after successful alarm treatment (e.g. achievement of 14 consecutive dry nights). Extra drinks are given at bed time to cause additional stress to the detrusor muscles in the bladder. Alarm treatment is then continued until fourteen consecutive dry nights are again achieved (4).

1.8.4 Multidimensional Behavioural Treatment Programmes

Multidimensional treatment programmes include Dry Bed Training and Full Spectrum Home Training (51). Dry Bed Training was initially developed in the early 1970s for use with people with learning disabilities (52). The original schedule involved an intensive training night, during which the patient was woken every hour and taken to the toilet. If an accident occurred, forty-five minutes of "cleanliness training" (changing the bed) and "positive practice" (patient practices getting up and going to the toilet about nine times) was implemented. On subsequent nights, the individual was woken once and taken to the toilet, this nightly wakening occurring progressively earlier. Because of inherent difficulties in implementing this regime it has been modified. Variants including Modified Dry Bed Training forgo the reprimands and positive practice elements (53)).

Full Spectrum Home Training combines urine alarm training, cleanliness training, retention control training (see under "Other" below) and over-learning procedures (54).

1.8.5 Psychotherapy

Because psychotherapists consider enuresis to be a symptom rather than a condition in itself, the emphasis of treatment is on the "child's inner emotional disturbance" (55). Consequently, the intervention is aimed at the underlying psychological causative factors and attempts to modify the environment which produced the symptom (55). Psychotherapy may be used in the management of children who have psychological problems in addition to enuresis, to address problems directly related to psychopathology (45).

1.8.6 Combined Psychological and Drug Interventions

There is a move towards combining psychological and drug interventions (51), the rationale being that the rapid onset of action of drugs is combined with the more gradual treatment effect of alarms (56). Using low doses of desmopressin as an adjunct to alarm treatment may also be used to ensure that the child only wets the bed once each night to minimise changes of bedding (40).

1.9 Other

1.9.1 Retention Control Training

This is an attempt to increase the functional bladder capacity using exercises such as delaying urination for extended periods of time or drinking increased fluids (45). Stream interruption exercises may also be recommended (57).

1.9.2 Surgery

Surgical treatments used for nocturnal enuresis include urethral dilation, meatotomy and bladder neck repair (28). Adverse effects of such interventions include urinary incontinence, recurrent epididymitis and aspermia (28) and surgery is not generally regarded as an appropriate treatment for bed wetting

1.9.3 Fluid Deprivation

This is a measure frequently implemented by parents (28). However, fluid restriction may aggravate a low functional bladder capacity (58). Even so, it might be useful to restrict drinks with diuretic properties prior to retiring (57).

1.9.4 Lifting

Lifting is another method often used. Carers "lift" the child, while still asleep, out of bed to allow them to urinate in an appropriate place. It has been argued that this practice is counterproductive for a number of reasons. These include the child being denied the opportunity to learn the sensations that a full bladder produces and the child being encouraged

to urinate without waking (36). On the other hand, some suggest that lifting is effective, precluding the need for professional help (28).

1.9.5 Wakening

This intervention involves waking the child to allow them to get up and urinate (45). A scheduled waking programme may be used with the child being woken progressively earlier after dry nights until the interval between going to bed and scheduled waking is one hour. Older individuals may use an alarm clock to wake themselves (4).

1.9.6 Complementary Interventions

Acupuncture (59-63), chiropractic (64-66) and homeopathy (67) are among the less orthodox approaches used to combat bed wetting.

The aims of this review are to systematically identify, appraise and summarise the results of rigorous evaluations of these interventions.

In addition to examining the overall evidence of effectiveness of the interventions, the review attempts to assess the degree to which effectiveness may differ for subsets of patients in order to better target treatments at the most appropriate client groups.

2 REVIEW METHODS

A systematic review was carried out in order to identify and appraise all relevant and rigorous evaluation studies, following national guidelines (371).

2.1 Search Strategy

A variety of sources were used to identify studies which evaluated of the effectiveness of interventions for nocturnal enuresis. The following electronic databases were searched using the strategies detailed in Appendix 1: AMED (alternative medicine); ASSIA (Applied Social Science Index); BIDS; BIOSIS Previews (1985-1996); CINAHL; DHSS Data; EMBASE (1974 to date); MEDLINE (1966 to date); PsycLIT and SIGLE. The searches were updated in July 1997, after the first draft had been completed, to identify any more recent publications. Thus this review covers the period 1966 to spring 1997. The reference sections of retrieved studies and review papers were also checked for further trials. Studies in any language were considered.

On-line searches do not necessarily locate all the relevant literature, so a number of other strategies have been used. Key organisations involved in the field of enuresis and manufacturers of enuresis products were contacted with requests for published and unpublished relevant information (see Appendix 2). Researchers, medical doctors, psychologists and other health professionals active in the enuresis field were similarly canvassed for information and to identify areas of uncertainty (Appendix 2).

2.2 Inclusion Criteria

Studies included in the review had to satisfy the following 3 criteria of relevance, outcome and study design.

2.2.1 Relevance

Only studies reporting evaluations of interventions used to remedy either primary or secondary non-organic nocturnal enuresis were considered. The non-organic basis (i.e., not due to any neurological disorder, to epileptic attacks, or to any structural abnormality of the urinary tract) should be demonstrated by medical examination or explicitly mentioned in the trial's own inclusion/exclusion criteria (68).

2.2.2 Outcomes

A set of outcome indicators has been devised for enuresis interventions (68) and are endorsed in the "Guidelines on minimum standards of practice in the intervention of enuresis" (39). These cover both short and long term effects. The outcomes are (a) initial success: the achievement of fourteen consecutive dry nights within a sixteen-week treatment period; (b) relapse: more than two wet nights in two weeks after initial success has been attained; c) continued success: no relapse in the six months after initial success and (d) complete success: no relapse in the two years after initial success. In addition, dropout has been defined as two consecutive appointments being missed without notice or discontinuation of treatment by agreement with parents, sufferer and clinician (69).

However, these definitions are based on the outcomes of behavioural interventions (68). Much medical literature reports reduction in wetting frequency rather than remission (70).

To be included in this review, studies had to have reported both
a) systematic measurement of baseline levels of wetting, e.g. number of wet nights in a period before intervention (68). Relying on parents' recall of their child's bed wetting frequency may result in an over estimation of the baseline level of wetting (71). In addition, some children cease to wet the bed once the frequency of wetting is monitored (28, 30).
b) outcomes, e.g., number of wet nights after intervention, number of participants achieving 14 consecutive dry nights.

2.2.3 Design

Well designed experimental studies in which the intervention group is compared with a comparable control group reduce bias and confounding. All randomised controlled trials meeting the relevance and outcome criteria were included. The main analysis involved randomised controlled trials (RCTs).

2.3 Exclusion Criteria

Studies of incontinence (wetting with underlying organic cause) and of encopresis (soiling) were excluded. Studies of interventions targeting only daytime wetting were also excluded.

2.4 Identification of Primary Studies

The titles and, where possible, abstracts of all studies located by the searches were independently checked by two reviewers to identify those likely to be evaluations of the effectiveness of interventions for nocturnal enuresis. Full papers were then obtained and independently assessed by two reviewers to identify those which met the inclusion criteria.

2.5 Assessments of Validity of Included Randomised Controlled Trials

A range of both general and more specific quality issues were assessed by two reviewers. The general quality items were: the level of concealment of allocation in randomised controlled trials; comparability of groups at baseline; use of a wash out period if a crossover design was employed; intention to treat analysis; whether outcomes were clearly defined; blinding; a follow up of at least three months; the use of appropriate statistical techniques and whether useful data (e.g. means and standard deviations) were presented. In addition, the trial's inclusion criteria were checked to see whether children with daytime wetting were specifically excluded.

2.6 Data Extraction

The data were extracted using a standard form (see Appendix 3). Where appropriate, the results were converted to the mean and standard deviation number of WET nights per WEEK. The forms were checked by a second reviewer.

2.7 Data Synthesis

A qualitative overview of all randomised controlled trials is presented and also, where possible, a quantitative synthesis calculating standardised effect sizes (weighted mean differences where variables are continuous and relative risks where outcomes were measured as binary) using the more conservative random effects model (372). This was performed using the Cochrane Collaboration's Metaview software. The weighted mean differences are weighted by sample size and give the differences in terms of number of wet nights per week. In some instances a pooled estimate of standard deviation has been calculated from the available standard deviations and used in those studies where the standard deviation was not reported. All randomised controlled trials where we used an estimated standard deviation are marked *. When it has not been possible to calculate confidence intervals, point estimates of the absolute differences in the mean number of wet nights per week in the two conditions are presented.

2.8 Investigations of Differences Between the Randomised Controlled Trials

Chi squared tests for heterogeneity were performed. Where significant heterogeneity was found (at the 10% probability level) or appeared obvious from visual inspection of the results, the differences between the randomised controlled trials were further investigated.

3 STUDIES INCLUDED IN THE REVIEW

Full details of included randomised controlled trials included in the review are given in the tables in Appendix 4. Excluded studies are given in Appendix 5.

3.1 Number of Studies Included

The various searches located 952 potentially relevant primary studies and reviews. Scrutiny of the titles and abstracts identified 302 possible evaluations of interventions used with enuresis, 116 of which were randomised controlled trials (RCTs). The total number of studies and RCTs meeting the inclusion criteria are given in Table 3.1.

Table 3.1: Studies meeting inclusion criteria

Inclusion criterion	All studies	RCTs
Evaluation of effectiveness of intervention for nocturnal enuresis	302	116
Organic causes of bed wetting excluded	189	91
Systematic baseline measurement of bed wetting	167	76
Systematic outcome measure of bed wetting	290	115
Meet all inclusion criteria		62

Some trials were published on more than one occasion - these duplicates are noted in the table of included studies (App 4). The RCTs came from all over the world and 10 foreign language papers are included. A breakdown of studies by country of origin, recruitment and also by year of publication is given in Appendix 6.

Only 17 RCTs explicitly excluded daytime wetting; in most RCTs diurnal enuresis was not mentioned and 7 RCTs included some children who also wet by day.

3.2 Quality of Included Studies

The results of the validity assessments of the included RCTs are summarised in Table 3.2 (further details in Appendix 7). Some RCTs considered more than one intervention so the total number of evaluations exceeds 62. The concealment of allocation refers to how well the allocation to treatment group was concealed. A indicates adequate concealment of allocation (e.g. by use of sealed opaque envelopes) B indicates uncertainty about whether the allocation was adequately concealed and C indicates that allocation was definitely not adequately concealed (e.g. quasi-randomisation such as alternate days).

Generally, the RCTs were not of high quality. In most the method of allocation was unclear; there was no indication of how comparable the groups were at baseline and few reported wash out phases in crossover trials. In general, sample sizes were small, ranging from 2 (an alarm group) to 125 (imipramine) but on average consisted of about 22 participants. Small sample sizes result in a failure to demonstrate significant differences between studies. Power calculations can be used to ascertain the sample sizes necessary to demonstrate a difference. Only two of the included RCTs included a power calculation (53, 72).

3.3 Outcomes

Four main outcomes have been used: mean frequency of wetting in a given time period; attainment of 14 consecutive dry nights (initial success); mean frequency of wetting at post treatment follow up and number of relapses. Although most trials reported the mean frequency of wetting, many did not report measures of dispersion. Reporting of initial success was more frequent in behavioural trials; 7/8 multi-dimensional behavioural treatment programmes and half the alarm treatment groups used this measure as compared with less than a quarter of desmopressin trials.

Table 3.2: Number of RCTs by quality indicators

Intervention	RCT	Conceal-ment of allocation	Compar-able groups at baseline	Washout period in cross over	Intention to treat	Blinding	Follow up for at least 3 months
desmopressin	18	2A 16B	8 yes	2	2 2 no dropout	16 double 1 single	5
imipramine	19	1A 13B 5C	5 yes	1	1 1 no dropout	14 double 1 single	6
other drugs	13	3A 9B 1C	5 yes	1	2 no dropout	7 double 1 single	4
star chart	0						
alarms	16	1A 12B 3C	10 yes	1	4 2 no dropout	3 double 1 single	13
multi-behav	8	6B 2C	4		3 1 no dropout		6
psychotherapy	0						
combined	2	1A 1B	1 yes	1	1 no dropout	2 double	2
retention	1	B	0	0	0	0	
surgery	0						
fluid deprivation	0						
lifting	0						
wakening	1	B	1			double	1
complementary	2	2B	0	0	0	0	1

Table 3.3: Outcome measures used

Intervention	RCT	Mean freq of wetting	Initial success	Mean freq of wetting (follow up)	Relapse	Means and SD reported
desmopressin	18	18	4	5	5	12
imipramine	19	15	2	4	2	6
other drugs	13	12	4	4	2	3
alarms	16	14	8	5	7	3
multi-behav	8	4	7	0	4	0
combined	2	2	0	1	0	1
retention	1	1	0	1	0	0
wakening	1	1	0	0	0	0
complementary	2	2	0	1	0	0

4 RESULTS OF THE REVIEW

Eighteen of the included RCTs evaluated the effectiveness of desmopressin as an intervention (1, 72-88). Nineteen of the included RCTs evaluated the effectiveness of imipramine (77, 89-106). However, one trial combined the results of the active and control group (106) and two trials stated that there were differences between the groups without presenting any data (90, 104).

Thirteen RCTs evaluated the effectiveness of other drugs. These were amitriptyline hydrochloride (75, 107), amphetamine sulphate (108), chloripramine (100) chlorprotixine (109); desipramine (110); desmopressin and amitriptyline mixture (75), ephedrine (95), ephedrine sulphate and atropine sulphate mixture (108); furosemide (Lasix) (99); meprobamate and hydroxyzine mixture (92); mianserin (105) oxybutynin (111); phenmetrazine (112) and viloxazine (89).

No RCTs were found which evaluated the effectiveness of star charts or rewards.

Sixteen RCTs involved an enuresis alarm component (1, 56, 91, 93, 100, 107, 108, 113-121).

Eight RCTs investigated Dry Bed Training (52, 53, 113, 114, 122-125). No RCTs of Full Spectrum Home Training were found which met all the inclusion criteria.

No RCTs involving a psychotherapy component met the inclusion criteria.

Two RCTs involving comparisons which included combined approaches met the inclusion criteria (56, 91).

One RCT investigated the effectiveness of bladder training without an alarm (126); two RCTs looked at retention control training as an adjunct to alarm treatment (115, 116).

No RCTs were found which evaluated the effectiveness of surgery on nocturnal enuresis.

No RCTs were found which evaluated the effectiveness of fluid deprivation on nocturnal enuresis.

No RCTs were found which evaluated the effectiveness of lifting on nocturnal enuresis.

One RCT compared random wakening with other treatments (91).

The effectiveness of chiropractic treatment was compared with a waiting list control group (127). Various trance conditions have been compared in a RCT (128).

4.1 Desmopressin

A summary of RCTs involving desmopressin is given in Table 4.1.

4.1.1 Desmopressin Compared with Placebo

Wet Nights Per Week at the End of Treatment

Fifteen RCTs compared the mean number of wet nights in desmopressin and placebo groups (72-76, 79-88). Two of these each contained details of two trials (81, 82). Pooled estimates of standard deviation from the 10 RCTs reporting measures of dispersion were used in RCTs where none could be obtained (marked *) (Table 4.1.1).

Weighted mean differences (WMD) and 95% confidence intervals were calculated for each RCT (Figure 4.1.1 a). Negative values indicate fewer wet nights in the desmopressin group.

The results of RCTs using the same dosage of desmopressin were combined using random effects method. In comparison with placebo groups, those treated with 10 μg of desmopressin had 2.2 fewer wet nights per week (95% CI: -3.7 to -0.7); those treated with 20 μg had 1.4 fewer wet nights per week (95% CI: -1.8 to -1.0) and those treated with 40 μg had 1.4 fewer wet nights per week (95% CI: -1.9 to -0.9). One trial combined the results of 10 μg and 40 μg doses (74), here the desmopressin group had 3.4 fewer wet nights than the placebo group (95% CI: -4.7 to -2.1).

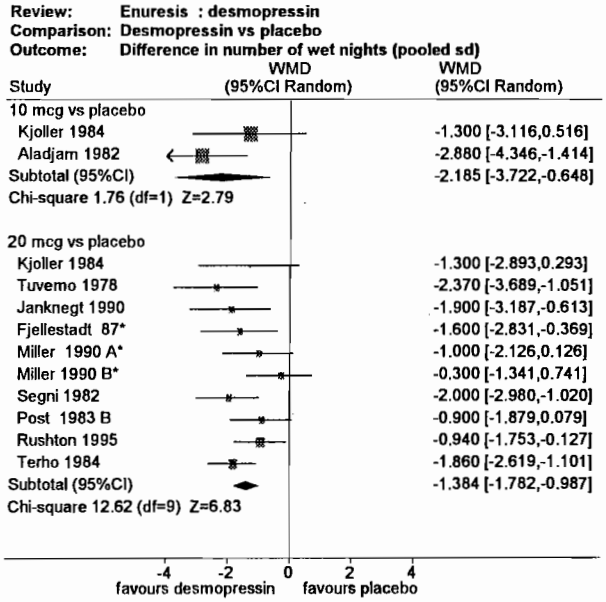
Table 4.1: RCTs including desmopressin

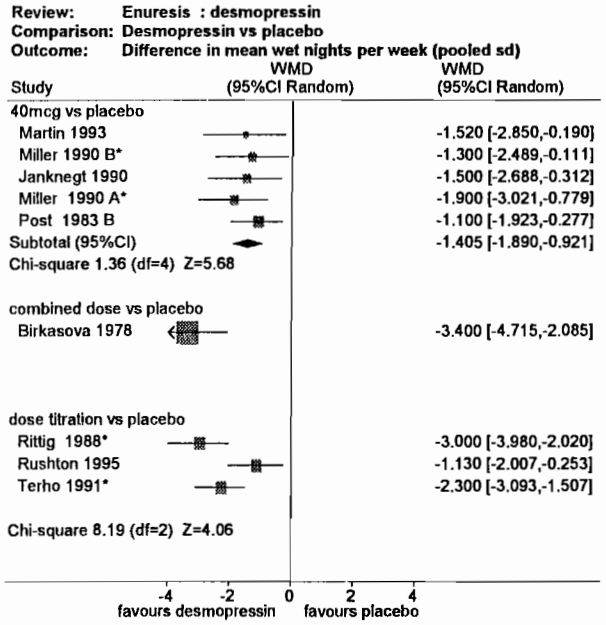
Study	Number in group		Intervention
Aladjem, 1982 (73)	A: 15 B: 15		A: desmopressin 10 µg B: placebo
Birkasova, 1978 (74)	22 crossover		A: desmopressin drops 10 µg B: desmopressin drops 40 µg C: placebo
Burke, 1995 (75)	A: 17 B: 14 C: 14		A: desmopressin 20 µg B: desmopressin 20 µg + amitriptyline 25 or 50 mg C: amitriptyline hydrochloride 25 or 50 mg
Fjellestad-Paulsen, 1987 (76)	19/20 crossover		A: desmopressin (oral) 200 µg B: desmopressin intranasal drops 20 µg C: placebo tablets D: placebo drops
Holt, 1986 (77)	A: 17 B: 19		A: desmopressin 20 µg B: imipramine 50 mg
Janknegt, 1990 (72)	22 crossover		A: desmopressin drops 20 µg B: desmopressin drops 40 µg C: placebo
Janknegt, 1997 (78)	A: 34 B: 32		A: desmopressin tablets: 200 µg B: desmopressin tablets: 400 µg
Kjoller, 1984 (79)	A: 13 B: 12 C: 12		A: desmopressin 10 µg B: desmopressin 20 µg C: placebo
Martin Hernandez, 1993 (80)	A: 22 B: 22		A: desmopressin drops 40 µg B: placebo
Miller, 1990 (81)	Centre 1 A: 19 B: 26 C: 31	Centre 2 A: 27 B: 24 C: 26	A: desmopressin acetate 20 µg B: desmopressin acetate 40 µg C: placebo
Post, 1983A (82)	52 crossover		A: desmopressin 40 µg B: placebo
Post, 1983B (82)	20 crossover		A: desmopressin 20 µg B: placebo
Rittig, 1988 (83)	34 crossover		A: optimum dose desmopressin (dose titration) B: placebo
Rushton, 1995 (84)	A: 49 B: 47		A: desmopressin spray 20 µg B: placebo
Segni, 1982 (85)	20 crossover		A: desmopressin 20 µg B: placebo
Terho, 1984 (86)	49/54 crossover		A: desmopressin drops 20 µg B: placebo
Terho, 1991 (87)	52 crossover		A: desmopressin 20 µg B: placebo
Tuvemo, 1978 (88)	18 crossover		A: desmopressin 20 µg B: placebo
Wille, 1986 (1)	A: 24/25 B: 22/25		A: intranasal desmopressin 20 µg B: alarm

Table 4.1.1: Pooled estimates of standard deviations used in the meta-analysis

	Pooled estimates of standard deviations			
			At follow up	
	Desmopressin	placebo	Desmopressin	placebo
20 µg	2.08	1.78	2.16	2.18
40 µg	2.29	1.97	2.16	2.18
combined/other	2.15	1.78	2.16	2.18

Figure 4.1.1a: Desmopressin vs placebo: weighted mean differences and confidence intervals





The 3 RCTs using "optimum" doses of desmopressin (as ascertained by a dose titration period) all showed improvements compared with placebo. However, their results were heterogenous ($\chi^2 = 9.10$) (Figure 4.1.1 a). This suggests that the three RCTs may have involved different populations of subjects. Therefore their results were not combined.

To further explore the differences between the RCTs comparing "optimum" doses of desmopressin with placebo, the details of the three RCTs were compared (Table 4.1.2). Estimates of standard deviation were used in two RCTs (83, 87). The RCT with the largest effect size (83) involved both children and adults and the severity of wetting was only expressed as a minimum of 3 wet nights per week - at least 2 wet nights a week less than the other RCTs.

Table 4.1.2: Exploration of the differences between RCTs investigating optimum doses of desmopressin and placebo

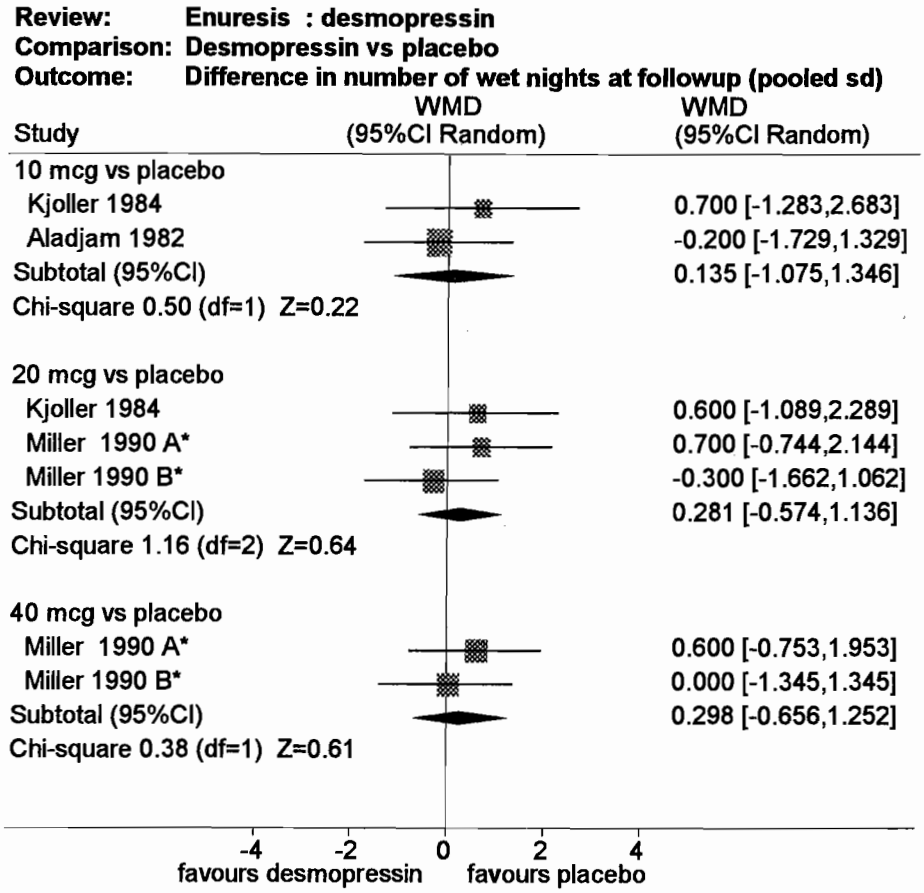
Study year	Country	Effect size (95% CI)	Sample size	Age	Diurnal wetting	Previous treatment	mean wet nights per week	Dropouts
Rushton, 1995 (84)	USA	-1.1 (-2.0, 0.3)	A: 49 B: 47	7 - 14	excluded	no details	5.5	none reported
Terho, 1991 (87)	Finland	-2.3 (-3.1,-1.5)	52 cross-over	range: 5 to 13 years	excluded	waking, fluid restriction, antidepressants alarm	6.4	None
Rittig, 1988 (83) 1988	Sweden	-3.0 (-4.0,-2.0)	34 cross-over	8 - 45	excluded	all failed previous treatment	3+ wet nights per week	no details

NB: negative results favour desmopressin

Wet Nights Per Week After Post Treatment Follow Up

Three of these RCTs compared the mean number of wet nights in the desmopressin and placebo groups when followed up after treatment had ceased (73, 79, 81). A pooled estimate of standard deviation from the two RCTs which reported measures of dispersion was used for the RCT where none could be obtained. Weighted mean differences (WMD) were calculated for each RCT (Figure 4.1.1 b) and the results were combined using a random effects models for each dose.

Figure 4.1.1 b: Desmopressin vs placebo: weighted mean differences and confidence intervals at post treatment follow up.



No difference was found between any of the doses of desmopressin and placebo in the mean number of wet nights per week at post treatment follow up.

Participants Achieving 14 Consecutive Dry Nights

Three of these RCTs compared the number of participants achieving 14 consecutive dry nights after taking either desmopressin or placebo (73, 76, 80). Relative risks (RR) have been calculated, giving a measure the likelihood of achieving 14 consecutive dry nights after treatment with different doses of desmopressin as compared with placebo (Table 4.1.3).

Table 4.1.3: Relative risks of achieving 14 consecutive dry nights: desmopressin vs placebo

Randomised controlled trial	RR (95% CI)
Combined dose vs placebo (Fjellestad-Paulsen, 1987) (76)	2.0 (0.2, 20.3)
10 µg desmopressin vs placebo (Aladjem, 1982) (73)	6.8 (0.9, 50.2)
40 µg desmopressin vs placebo (Martin Hernandez, 1993) (80)	5.0 (0.6, 39.4)
Pooled	4.6 (1.4, 15.0)

Each study showed that participants were more likely to achieve 14 dry nights with desmopressin than with placebo. However, none of the estimates were statistically significantly different from zero. When the RCTs were combined thus increasing the power of the analysis, the pooled estimate showing that participants are over 4 times more likely to achieve 14 consecutive dry nights after taking desmopressin than placebo, the result was statistically significant. There was no evidence of heterogeneity at the 10% level.

Participants Relapsing

None of the RCTs looked at relapse rates.

4.1.2 Other Desmopressin Comparisons

Three RCTs directly compared different doses of desmopressin (72, 79, 81). The numbers of wet nights per week were very similar for the high and low doses both during treatment and at post treatment follow up (Table 4.1.4).

Table 4.1.4: Low dose vs high dose of desmopressin: weighted mean differences and confidence intervals during treatment and at post treatment follow up

RCT	**Mean number of dry nights per week** **WMD (95% CI)**	**Mean number of dry nights per week at follow up** **WMD (95% CI)**
10 µg vs 20 µg desmopressin (Kjoller, 1984) (79)	0.00 (-1.72, 1.72)	0.1 (-1.85, 2.05)
20 µg vs 40 µg desmopressin		
(Janknegt, 1990) (72)	-0.4 (-1.79, 0.99)	
(Miller, 1990)A* (81)	0.9 (-0.38, 2.18)	-0.3 (-1.66, 1.06)
(Miller, 1990)B* (81)	1.0 (-0.30, 1.4)	0.1 (-1.18, 1.38)
Pooled	0.6 (-0.30, 1.40)	-0.1 (-1.02, 0.84)

No statistically significant difference was found between the mean number of wet nights per week for participants treated with either oral or nasal desmopressin during treatment WMD: 0.1 (95% CI: -1.4 to 1.6) or the number achieving 14 consecutive dry nights RR: 2.0 (95% CI: 0.2 to 20.3) (76).

4.1.3 Desmopressin compared with other drugs

Single RCTs have compared desmopressin (20 μg) with desmopressin plus amitriptyline and amitriptyline hydrochloride (75) and also in comparison with imipramine (Table 4.1.5) (77). The differences in numbers of wet nights per week were similar in each of the comparisons, however this reached statistical significance for the desmopressin against amitriptyline comparison. The numbers of wet nights per week at post treatment follow up and numbers attaining 14 consecutive dry nights and relapsing were also similar.

Table 4.1.5: Comparisons of desmopressin and other drugs

Comparison	Difference in wet nights per week: WMD (95% CI)	Difference in wet nights per week at post treatment follow up: WMD (95% CI)	Number achieving 14 consecutive dry nights: RR (95% CI)	Number relapsing: RR (95% CI)
desmopressin vs amitriptyline (Burke, 1995) (75)	1.4 (0.1, 2.7)		0.3 (0.03, 2.4)	
desmopressin vs amitriptyline + desmopressin (Burke, 1995) (75)	1.4 (-0.1, 2.9)		0.2 (0.03, 1.6)	1.3 (0.8, 1.9)
desmopressin vs imipramine (Holt, 1986) (77)	-0.1 (-1.5, 1.3)	0.2 (-1.6, 1.2)		

4.2 Imipramine

A summary of the RCTs involving imipramine is given in Table 4.2

Table 4.2: RCTs including imipramine

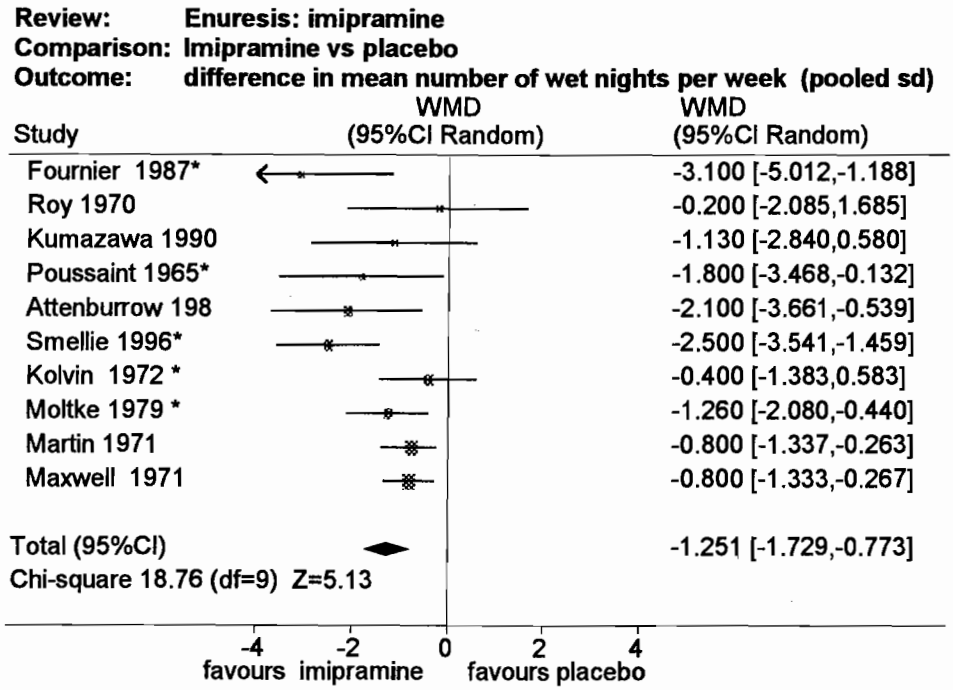
Author	Number in group	Intervention
Attenburrow, 1984 (89)	A: 12 B: 9 C: 12	A: imipramine 50 - 75 mg B: viloxazine 100 - 150 mg C: placebo
Bindelglas, 1968 (90)	63	A: imipramine 25-50 mg B: placebo
Fournier, 1987 (91)	A: 8 B: 8 C: 8 D: 8 E: 8	A: imipramine (mean dose 125 mg) B: placebo C: alarm D: random wakening E: alarm + imipramine
Ingle, 1968 (92)	A: 12 B: 13	A: imipramine 25 - 50 mg B: meprobamate and hydroxyzine
Kolvin, 1972 (93)	A: 35 B: 32 C: 27	A: imipramine (dose not stated) B: alarm C: placebo
Kumazawa-Ichikawa, 1990 (94)	A: 10 B: 10	Motivational reinforcement and bladder exercises followed by A: imipramine 25 mg B: placebo
Kunin, 1970 (95)	18 crossover	A: imipramine hydrochloride 25-50 mg B: ephedrine sulphate 7.5 - 15 mg
Manhas, 1967 (96)	A: 29 B: 27	A: imipramine 25 mg B: placebo
Martin, 1971 (97)	57 crossover	A: imipramine pamoate 10 mg B: imipramine pamoate 25 mg C: placebo
Maxwell, 1971 (98)	125/135	A: imipramine 25 - 50 mg + star chart B: placebo + star chart
Moltke, 1979 (99)	A: 43 B: 44	A: imipramine 25 - 75 mg B: Furosemide (Lasix) 40 - 80 mg C: placebo
Motavalli, 1994 (100)	A: 10 B: 9 C: 10	A: imipramine 10 - 25 mg B: clomipramine 10 - 25 mg C: placebo
Poussaint, 1965 (101)	A: 10 B: 11	A: imipramine 25 - 50 mg B: placebo
Roy, 1970 (102)	A: 14 B: 6 C: 6	A: imipramine 25 mg B: placebo C: no treatment control
Schroder, 1971 (103)	A: 35 B: 27	A: imipramine 30 mg B: placebo
Shaffer, 1968 (104)	59/81	A: imipramine 50 mg B: imipramine 75 mg C: placebo
Smellie, 1996 (105)	A: 25 B: 26 C: 29	A: imipramine 25 mg B: mianserin 10 mg C: placebo
Thomsen, 1967 (106)	19/30	A: imipramine 25 - 50 mg B: placebo

4.2.1 Imipramine Compared with Placebo

Wet Nights Per Week at the End of Treatment

Ten RCTs compared imipramine and placebo in terms of the mean number of wet nights per week (89, 91, 93, 94, 97-99, 101, 102, 105). Where no measure of dispersion could be obtained, pooled estimate of standard deviations were imputed (imipramine sd = 1.90, placebo sd = 2.00) from the three RCTs where they were reported (94, 97, 98). Weighted mean differences (WMD) were calculated for each RCT (Figure 4.2.1 a). When the results of RCTs were combined using a random effects model, participants treated with imipramine had around one less wet night per week than those given placebo: WMD = -1.3 (95% CI -1.8 to -0.7).

Figure 4.2.1a: Imipramine vs placebo: weighted mean differences and confidence intervals



The results of these RCTs are, however, heterogeneous at the 10% probability level (Figure 4.2.1a). To further explore the differences in effect size between the RCTs, the two trials with the largest effect sizes (91, 105) were compared with the two trials with the smallest effect sizes (93, 102) (Table 4.2.1).

Table 4.2.1: Exploration of the differences between RCTs comparing imipramine and placebo showing high and low effect sizes

	Trial	Dose	Effect size (95% CI)	Sample size	Age	Severity (mean wet /week)	Drop outs
large effect size	Fournier, 1987 (91)	mean 125 mg	-3.1 (-5.0, -1.2)	A: 8 B: 8	Mean age: 8 y 5m	A: 5.3 B: 4.5	no details
	Smellie, 1996 (105)	25 mg	-2.5 (-3.5, -1.5)	A: 25 B: 29	5 to 13 years	A: 5.4 B: 6.0	0
small effect size	Kolvin, 1972 (93)	no details	-0.4 (-1.4, 0.6)	A: 35 B: 27	9 y 4m (range 8 to 10)	A: 5.7 B: 5.2	2
	Roy, 1970 (102)	25 mg	-0.2 (-2.1, 1.7)	A: 14 B: 6 at deaf & dumb school	7 to 17 yrs	A: 4.2 B: 3.1	No details

NB: negative results favour imipramine

No obvious differences were found between the RCTs with the largest and smallest effect sizes. The heterogeneity is likely to be due to random variation.

Two trials provided no raw data: one stated that imipramine performed significantly better than placebo (90); the other found that 15 of the 17 participants showed the "appropriate rise and fall of dry nights" with imipramine (104).

Wet Nights Per Week After Post Treatment Follow Up

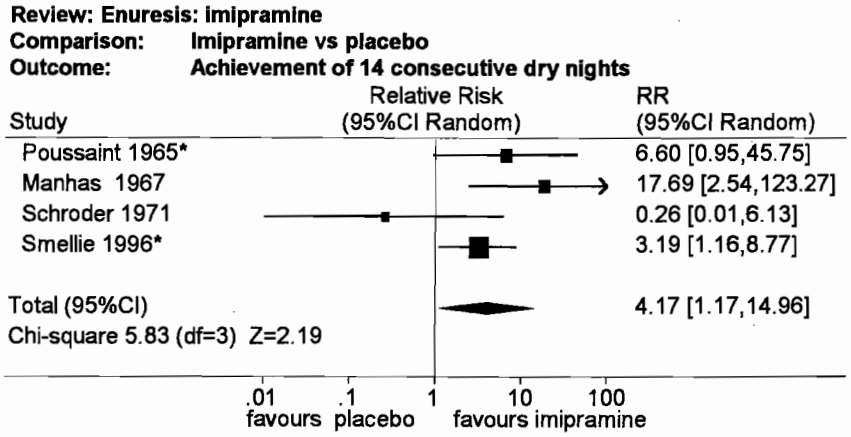
Neither of the RCTs presenting the mean number of wet nights at post treatment follow up reported measures of dispersion (89, 93). One trial found imipramine resulted in 1.5 fewer wet nights per week (absolute difference) than placebo (89); the other found placebo resulted in 0.6 fewer wet nights per week (absolute difference) than imipramine (93).

Participants Achieving 14 Consecutive Dry Nights

Four RCTs compared the number of participants achieving 14 consecutive dry nights after taking either imipramine or placebo (96, 101, 103, 105). Relative risks were calculated, giving a measure of the likelihood of achieving 14 consecutive dry nights after treatment with

imipramine as compared with placebo (Figure 4.2.1b). Participants treated with imipramine were 4 times more likely to attain fourteen consecutive dry nights than those receiving placebo: RR = 4.2 (95% CI: 1.2 to 15.0). The χ^2 test of heterogeneity was not significant at the 10% level.

Figure 4.2.1b: Relative risks of achieving 14 consecutive dry nights: imipramine compared with placebo.



Participants Relapsing

None of the RCTs looked at relapse rates.

4.2.2 Other Imipramine Comparisons

Two RCTs compared different doses of imipramine (97, 104). One RCT stated that there was no difference between the two doses (104). Participants receiving 25 mg of imipramine pamoate had 0.9 (95% CI: 0.39 to 1.41) fewer wet nights than those receiving 10 mg (97).

4.2.3 Imipramine Compared with Other Drugs

Six RCTs compared imipramine with other drugs (Table 4.2.2), three of which reported measures of dispersion (92, 95, 100). Participants treated with imipramine had 4.6 (95% CI: -6.00, -3.2) fewer wet nights per week than those treated with meprobamate plus hydroxyzine (92) and 2.1 (95% CI: -3.1, -1.0) fewer wet nights per week than those treated with ephedrine sulphate (95). Imipramine produced only 1.2 (95% CI: -3.2, 0.8) fewer wet nights per week than chlomipramine, the confidence interval including zero (100). The absolute differences in the mean number of wet nights per week in the other trials are given in Table 4.2.2

Table 4.2.2: Comparisons of imipramine and other drugs

Comparison	**Difference in mean number of wet nights per week (95% CI)**
imipramine vs meprobamate + hydroxyzine (Ingle, 1968) (92):	-4.6 (-5.96, -3.24)
imipramine vs ephedrine sulphate (Kunin, 1970) (95)	-2.1 (-3.1, -1.02)
imipramine vs clomipramine (Motavalli, 1994) (100)	-1.2 (-3.19, 0.79)
imipramine vs mianserin (Smellie, 1996) (105)	-2.5 (absolute difference)
imipramine vs furosemide (Moltke, 1979) (99)	-1.68 (absolute difference)
Imipramine vs viloxazine (Attenburrow, 1984) (89)	1.00 (absolute difference)

Participants in the imipramine group were nearly 4 times more likely to attain fourteen consecutive dry nights than those in the mianserin group (105): RR =3.81(95% CI: 1.20, 12.07).

4.3 Other Drug Interventions

In addition to the RCTs discussed above (75, 89, 92, 95, 99, 100, 105), 6 additional trials involved other drugs. These are summarised in Table 5.3

Table 4.3: RCTs involving other drugs

	Number in group	Intervention
Danquah, 1975 (107)	A: 10 B: 10 C: 10	A: amitriptyline hydrochloride 10 - 25 mg B: enuresis alarm C: traditional shaming
Gjessing, 1968 (109)	69 crossover	A: chlorpotixine 5 mg B: placebo
Harrington, 1960 (112)	10/11 crossover	A: Phenmetrazine 25 mg B: placebo
Liederman, 1969 (110)	A: 53 B: 47	A: desipramine 50 - 75 mg B: placebo
Lovering, 1988 (111)	41 crossover	A: oxybutynin 10 mg B: placebo
Wright, 1974 (108)	A: 3/3 B: 5/5 C: 2/5 D: 10/10	A: amphetamine sulphate 2.5 mg at bed time B: ephedrine sulphate 7.5 mg + atropine sulphate 1.15 mg (Enuretrol) morning and night C: alarm D: placebo

4.3.1 Other Drugs Compared with Placebo

Wet Nights Per Week at the End of Treatment

Five RCTs compared of the mean number of wet nights of five different drugs and placebos conditions (Table 4.3.1) one of which combined the results of two active preparations (108). However, only one trial (112) reported measures of dispersion which allowed weighted mean differences and confidence intervals to be calculated. Phenmetrazine produced only 1 fewer wet night per week than placebo (95% CI: -2.52 to 0.52) (112). Table 4.3.1 gives the differences in the number of wet nights between the active and placebo conditions for the RCTs involving other drugs.

Table 4.3.1: Other drugs vs placebo: weighted mean differences and absolute differences

Comparison	Difference in mean number of wet nights per week (95% CI)
phenmetrazine vs placebo (Harrington, 1960) (112)	-1.0 (-2.52, 0.52)
mianserin vs placebo (Smellie, 1996) (105)	-3.1 (absolute difference)
oxybutynin vs placebo (Lovering, 1988) (111)	-1.87 (absolute difference)
furosemide vs placebo (Moltke, 1979) (99)	0.0 (absolute difference)
viloxazine vs placebo (Attenburrow, 1984) (89)	0.42 (absolute difference)
amphetamine sulphate/ephedrine sulphate vs placebo (Wright, 1974) (108)	0.6 (absolute difference)

Wet Nights Per Week After Post Treatment Follow Up

Only one RCT gave the mean number of wet nights when followed up. Viloxazine resulted in 2.8 fewer wet nights per week than placebo (absolute difference) when followed up 2 weeks after treatment had ceased (89)

Participants Achieving 14 Consecutive Dry Nights

Only two trials looked at the number of participants achieving 14 consecutive dry night (105, 110). Desipramine was 3.55 times more likely than placebo to result in 14 consecutive dry nights (95% CI: 1.07, 11.81) (110). Mianserin and placebo treatment were equally likely to result in 14 consecutive dry nights: RR: 0.84 (95% CI: 0.21, 3.39) (105).

Participants Relapsing

None of the comparisons of other drugs with placebo presented relapse rates.

4.3.2 Other Drug Comparisons

Amitriptyline hydrochloride and amitriptyline plus desmopressin resulted in the same number of wet nights per week: WMD= 0.00 (95%CI: -1.55 to 1.55), number of participants achieving 14 consecutive dry nights: RR = 0.91 (95% CI: 0.24 to 3.41) and number of participants relapsing: RR: 1.33 (95% CI: 0.76 to 2.35) (75).

4.4 Enuresis Alarms

Nine RCTs involving enuresis alarms were found in addition to drug trials which included an alarm group (1, 93, 100, 107, 108) which have been referred to above in Tables 4.1, 4.2 and 4.3. These are summarised in Table 4.4.

4.4.1 Alarms Compared With Placebo/No Treatment Control

None of the included trials compared an alarm with an equivalent control treatment e.g. a non-functioning alarm. However, four RCTs involved comparisons of alarm and no treatment or waiting list control conditions (114, 117, 119, 121) and three compared alarms with a placebo drug (91, 93, 108).

Wet Nights Per Week at the End of Treatment

Six RCTs presented the mean number of wet nights at the end of treatment (Table 4.4.1) (91, 93, 108, 114, 117, 121). None of the trials gave measures of dispersion so only absolute differences are given (Figure 4.4.1). In all cases the alarm reduced the number of wet nights per week as compared with no treatment control.

Table 4.4: RCTs involving an enuresis alarm

Author	Number in group	Intervention
Bollard, 1981A (114)	A: 15/15 B: 12/15 C: 15/15	A: alarm - supervised B: alarm - unsupervised C: waiting list control
Bollard, 1981B (114)	A: 20/20 B: 20/20 C: 20/20 D: 20/20 E: 8/20 F: 20/20	A: alarm B: DBT - therapist at home C: DBT - therapist in hospital D: DBT - parents as therapist at home E: DBT - parents as therapists at home no alarm F: waiting list control
Butler, 1990A (113)	A: 17/20 B: 18/20	A: pad and bell alarm B: body-worn alarm
Fielding, 1980 (115)	34/45	A: alarm B: RCT + alarm
Geffken, 1986 (116)	40/50	A: alarm B: alarm + RCT
Jehu, 1977 (117)	A: 19 B: 20	A: alarm B: no treatment control
Sloop, 1973 (119)	A: 21 B: 21	A: alarm B: no treatment control
Taylor, 1975 (120)	61/82	A: Continuous alarm B: intermittent alarm C: over learning
Wagner, 1982 (129)	A: 13 B: 13 C: 13	A: contiguous alarm B: delayed response alarm C: waiting list control

Table 4.4.1: Alarm vs control: Absolute difference in mean number of wet nights

RCT	Mean number of wet nights per week
Alarm vs no treatment control Bollard 1981 (114) Jehu et al 1977 (117) Wagner et al 1985 (121)	 -3.8 (absolute difference) -5.0 (absolute difference) -4.7 (absolute difference)
Delayed alarm vs no treatment control Wagner, 1985 (121)	 -3.7 (absolute difference)
Unsupervised alarm vs control Bollard 1981 (114)	 -2.4 (absolute difference)
Alarm vs placebo Fournier 1987 (91) Kolvin 1971 (93) Wright 1974 (108)	 -2.5 (absolute difference) -0.4 (absolute difference) -1.8 (absolute difference)

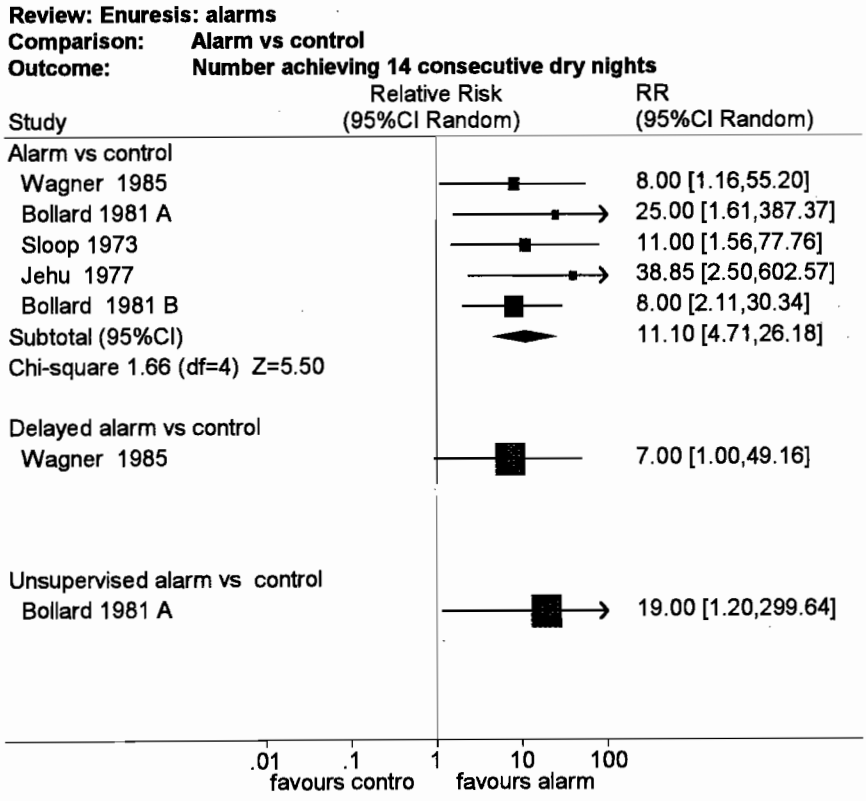
Wet Nights Per Week After Post Treatment Follow Up

One RCT gave post-treatment follow up results (93) - the alarm resulted in 0.5 (absolute difference) fewer wet nights per week than placebo.

Participants Achieving 14 Consecutive Dry Nights

Four RCTs compared the number of participants achieving 14 consecutive dry nights after alarm treatment with no treatment control (114, 117, 119, 121) (Figure 4.4.1). Relative risks have been calculated. When the results were combined, participants receiving alarm treatment were thirteen times more likely to achieve fourteen consecutive dry nights than the control group,: RR: 13.3 (95%CI: 5.6 to 31.5). The χ^2 test of heterogeneity was not significant at the 10% level.

Figure 4.4.1: Relative risks of achieving 14 consecutive dry nights: alarm compared with no treatment control



Participants treated with delayed alarms were 7 times more likely to attain 14 consecutive dry nights than the control group (95% CI: 1.0, 49.2) (121) and those whose alarm treatment was unsupervised were 19 times more likely to attain this than the control groups (95% CI: 1.2 to 300.0) (114). In both trials the confidence intervals are very wide.

Participants Relapsing

Relapse rates are rarely reported for control groups because few participants attain the required fourteen consecutive dry nights to start with. Only one RCT (114) reported relapse rates for the control group (consisting of two participants): RR: 0.38 (95% CI: 0.2 to 0.7).

4.4.2 Other Comparisons Between Alarms

Three RCTs investigated different alarm schedules (113, 120, 121). No measures of dispersion were given.

Table 4.4.2: Other alarm comparisons

Comparison	Wet nights per week	Relative risk (95%CI) of 14 consecutive dry nights	Relative risk (95%CI) of relapse
contiguous vs delayed alarm (Wagner, 1985) (121)	-1.05 (absolute difference)	1.14 (0.59, 2.22)	0.35 (0.10, 1.27)
bed vs body alarm (Butler, 1990) (113)		1.00 (0.67, 1.5)	1.00 (0.31, 3.23)
continuous vs intermittent alarm (Taylor, 1975) (120)		1.24 (0.7, 2.19)	1.56 (0.69, 3.52)

When the relative risks of 14 consecutive dry nights or number relapsing were calculated, no statistically significant difference was found (confidence intervals all contained 1) (Table 4.4.2), however, each comparison is based on a single small trial which lacked statistical power.

4.4.3 Alarms Compared With Augmented Alarm Programmes

Alarms may be supplemented by other behavioural programmes. How does this affect their effectiveness?

Wet Nights Per Week at the End of Treatment

The mean number of wet nights per week was considered in three trials involving augmented alarm treatment (Table 4.4.3), one of which reported measures of dispersion.

Table 4.4.3: Alarms compared with augmented alarms - difference in mean number of wet nights per week

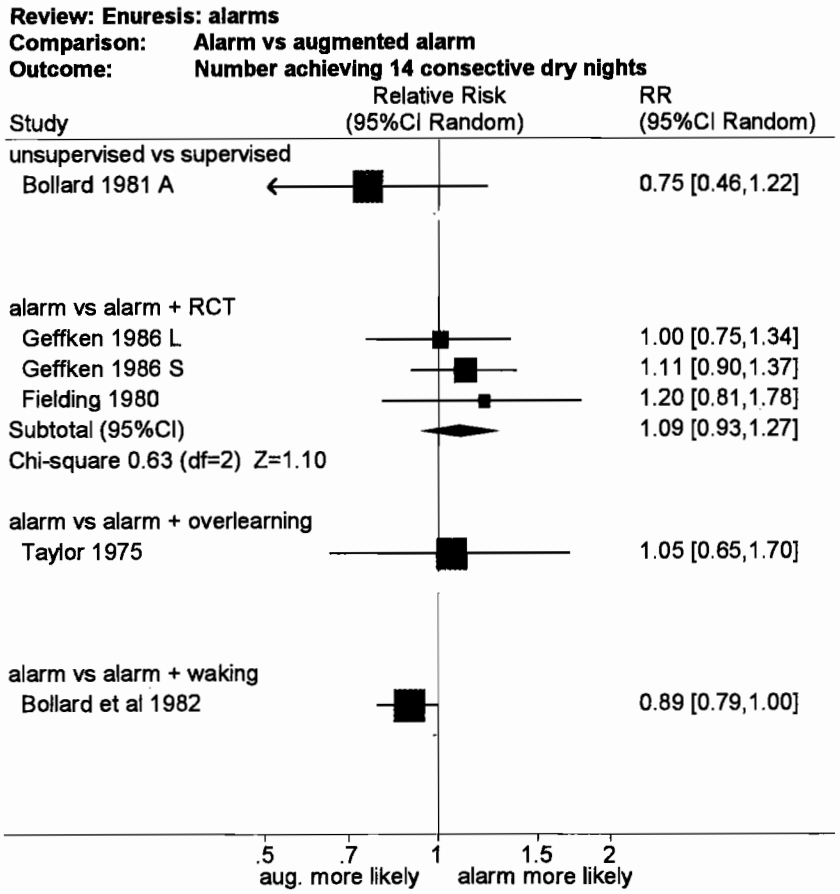
Comparison	Mean number of wet nights per week
unsupervised vs supervised alarm (Bollard 1981) (114)	1.4 (absolute difference)
alarm vs alarm + retention control training	
Fielding (1980) (115)	-0.9 (absolute difference)
Geffken (1986) (116) large functional bladder capacity	-0.8 (-1.73, 0.13)
Geffken (1986) (116) small functional bladder capacity	0.7 (-0.22, 1.62)

Neither supplementation of the alarm by supervision nor by retention control training significantly altered the resulting mean number of wet nights per week.

Participants Achieving 14 Consecutive Dry Nights

Participants were equally likely to attain 14 consecutive dry nights whether they were treated by alarm alone or alarm augmented by supervision (114); retention control training (115, 116); over-learning (120) or a wakening schedule (124) (Figure 4.4.3a)

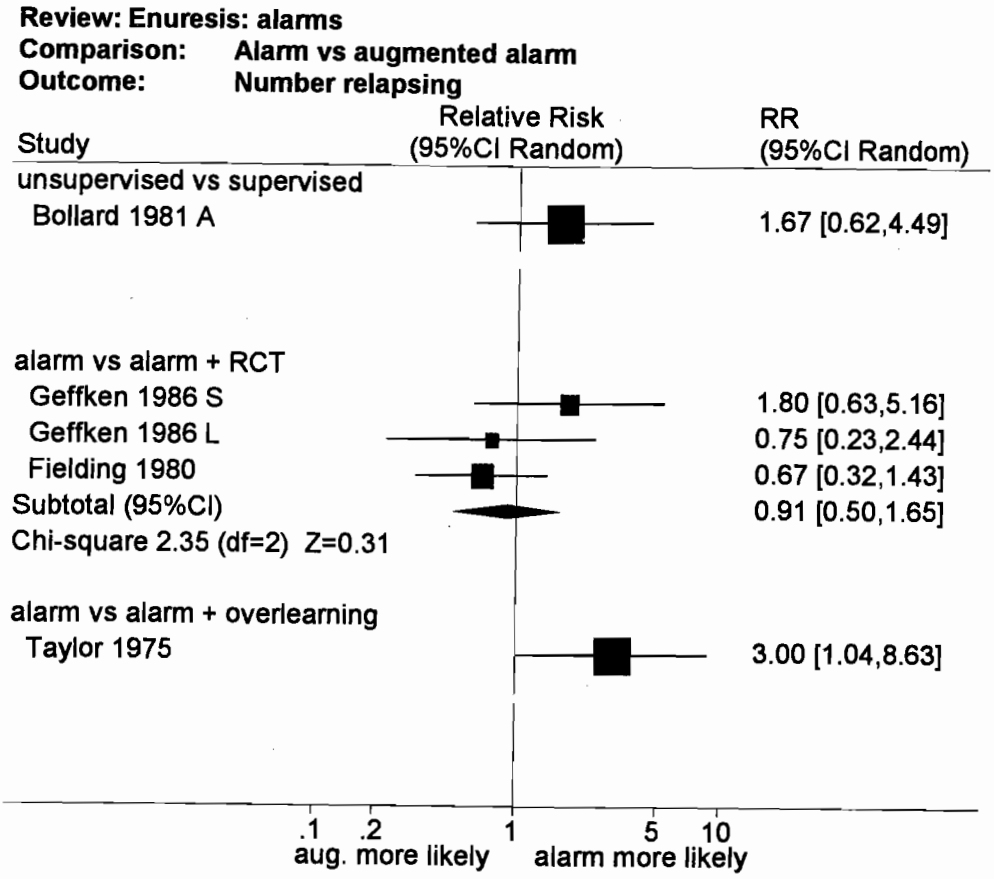
Figure 4.4.3a: Alarms compared with augmented alarms - participants achieving 14 consecutive dry nights



Participants Relapsing

Neither addition of supervision (114) nor retention control training (115, 116) to alarm treatment altered the relapse rates (Figure 4.4.3b). However, participants who received alarm treatment alone were three times more likely to relapse than those who received alarm treatment augmented by an over-learning schedule: RR = 3 (95% CI: 1.0 to 8.6) (120).

Figure 4.4.3b: Alarms compared with augmented alarms - participants relapsing



4.4.4 Alarm Compared With Other Psychological Interventions

A RCT carried out in Ghana compared alarm treatment with ritual shaming. This involved being carried from home by a singing mob and being thrown into the lagoon (107). Alarm treatment produced 2.4 (absolute difference) fewer wet nights per week than ritual shaming.

4.4.5 Relapse Rates With Alarms

As seen above (Figure 4.4.3), it is difficult to compare relapse rates of alarms with control groups. However, it is important to consider how many of those who initially attain 14 consecutive dry nights resume wetting. Table 4.4.4 gives the percentage of those in each group who resume wetting after varying follow up periods for the alarm treatments reported above.

Table 4.4.4 Relapse rates (%) for behavioural interventions

		3 months		6 months	12 months	12+ months
Bollard, 1981 (114) A	A: alarm - supervised B: alarm - unsupervised C: waiting list control				A: 4/12 (33) B: 5/9 (56)	
Butler, 1990 (113) A	A: pad and bell alarm B: body-worn alarm			A: 4/14 (29) B: 3/14 (21)		
Fielding, 1980 (115)	A: alarm B: retention control training + alarm	A: 4/14 (29) B: 3/11 (27)		A: 5/14 (36) B: 3/11 (27)	A: 8/14 (57) B: 4/11 (36)	
Geffken, 1986 (116)	A: alarm B: alarm + retention control training	large MFBC A: 3/9 (33) B: 4/9 (44)	Small MFBC A: 6/10 (60) B: 3/9 (33)			
Jehu, 1977 (117)	A: alarm B: control			A: 3/18 (17)		
Sloop, 1973 (119)	A: alarm B: no treatment control					4/11 (36)
Taylor, 1975 (120)	A: Continuous alarm B: intermittent alarm C: over learning	A: 9/13 (69) B: 4/9 (44) C: 3/13 (23)				
Wagner, 1982 (129)	A: contiguous alarm B: delayed alarm C: control			A: 2/8 (25) B: 5/7 (71)		

At three months relapse rates for enuresis alarms ranged from 29 to 69%.

4.5 Multidimensional Behavioural Treatment Programmes

In addition to (114) discussed above, 7 RCTs involving multidimensional behavioural programmes were found. These are summarised in Table 4.5

Table 4.5 RCTs of Multidimensional Behavioural Treatment Programmes

Author	Number in group	Intervention
Azrin, 1973 (52)	12	A: dry bed training B: alarm
Bollard, 1982 (122)	A: 60 B: 35	A: dry bed training + alarm B: alarm
Bollard, 1982 (124)	A: 10 B: 10 C: 10	A: dry bed training + alarm B: dry bed training C: no treatment control
Bollard, 1982 (123)	A: 12 B: 12 C: 12 D: 12 E: 12 F: 12	A: alarm + waking schedule B: alarm + retention control training C: alarm + positive practice + cleanliness training D: alarm + waking + retention control training E: alarm + waking + positive practice + cleanliness training F: alarm + retention control training + positive practice + cleanliness training
Butler, 1990B (113)	A: 23/24 B: 22/24	A: dry bed training - M B: body worn alarm
Butler, 1988 (53)	A: 29/35 B: 20/28	A: dry bed training - M + alarm B: alarm
Keating, 1983 (125)	A: 7 B: 9 C: 7 D: 7	A: dry bed training - office training parent + child B: dry bed training - home training parent + child C: dry bed training - office training parent only D: waiting list control

4.5.1 Comparison With No Treatment Control

Three RCTs compared Dry Bed Training (DBT) with a no treatment control group (114, 124, 125).

Wet Nights Per Week at the End of Treatment

Various training situations were compared with no treatment (125). Dry Bed Training with and without an alarm was also studied (124). Neither RCT reported measures of dispersion.

Table 4.5.1: Multidimensional Behavioural Treatment Programmes vs no treatment control: Absolute differences in mean number of wet nights per week

Comparison	Absolute difference
DBT- office training with parent and child vs no treatment control (Keating, 1983) (125)	0.7
DBT- home training with parent and child vs no treatment control (Keating, 1983) (125)	0.5
DBT- office training with parent only vs no treatment control (Keating, 1983) (125)	-0.1
DBT (with alarm) vs no treatment control (Bollard, 1982) (124)	-5.1
DBT (no alarm) vs no treatment control (Bollard, 1982) (124)	-0.6

DBT = Dry bed training

Wet Nights Per Week After Post Treatment Follow Up

None of the included RCTs reported the mean number of wet nights at follow up.

Participants Achieving 14 Consecutive Dry Nights

Only one trial gave the number of participants in both the Dry Bed Training and control group who attained 14 consecutive dry nights. Participants receiving Dry Bed Training (including an alarm) were 10 times more likely to attain 14 consecutive dry nights than the control group (95% CI: 2.7, 37.2) regardless of specifics of the training situation (114). Participants receiving Dry Bed Training without an alarm and those in the control group were equally likely to attain 14 consecutive dry nights. In all cases the confidence intervals are wide (Table 4.5.2).

Table 4.5.2: Multidimensional Behavioural Treatment Programmes vs no treatment control: Relative risks of achieving 14 consecutive dry nights and relapse

	RR of 14 consecutive dry nights	RR of relapse
DBT: therapist at home vs control (Bollard, 1981) (114)	10.0 (2.69, 37.24)	0.1 (0.03, 0.37)
DBT: therapist at home vs control (Bollard, 1981) (114)	10.0 (2.69, 37.24)	0.25 (0.12, 0.53)
DBT: therapist at hospital vs control (Bollard, 1981) (114)	10.0 (2.69, 37.24)	0.20 (0.08, 0.48)
DBT (no alarm) vs control (Bollard, 1981) (114)	2.5 (0.55, 11.41)	0.40 (0.14, 1.17)

Participants relapsing

One RCT provided relapse rates for both treatment and control groups (114). The participants given training involving alarms were less likely to relapse than no treatment control groups (Table 4.5.2). The risk of relapsing was similar for those given Dry Bed Training without an alarm and the no treatment control group.

4.5.2 Multidimensional Behavioural Treatment Programme Compared with Alarm

Five RCTs compared Dry Bed Training including an alarm with alarm alone (52, 53, 113, 114, 124).

Wet Nights Per Week at the End of Treatment

Two RCTs compared Dry Bed Training (DBT) using an alarm with alarm alone (53, 114) - neither gave measures of dispersion. In one RCT the DBT group had 4.4 fewer wet nights per week (absolute difference) than the alarm group (114); in the other the DBT had 0.75 fewer wet nights per week (53).

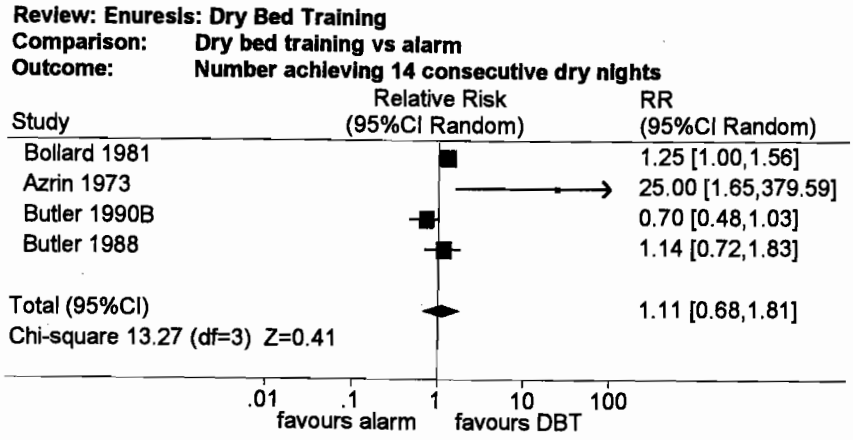
Wet Nights Per Week After Post Treatment Follow Up

None of the included RCTs reported the mean number of wet nights at follow up.

Participants Achieving 14 Consecutive Dry Nights

Only one RCT found DBT resulted in more patients achieving 14 consecutive dry nights than alarm treatment alone (52); the other three trials found no difference between the conditions (Figure 4.5.2). When all four trials were pooled, DBT and alarm treatment were equally likely to result in 14 consecutive dry nights: RR: 1.1 (95% CI: 0.7 to 1.8). Not surprisingly, the test for heterogeneity was significant at the 10% level.

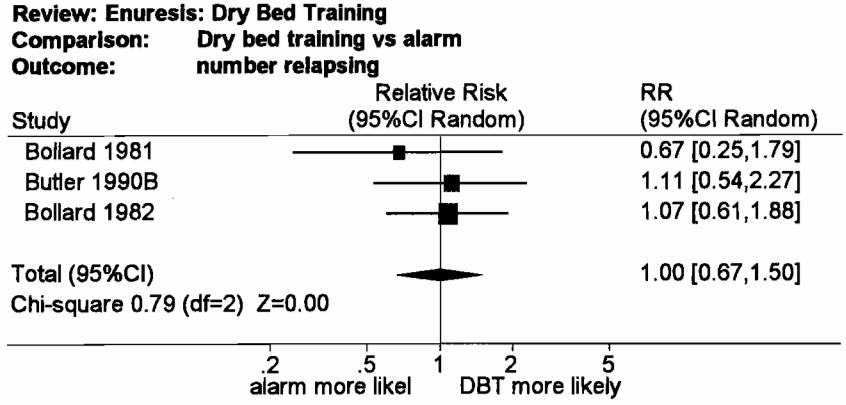
Figure 4.5.2: Dry Bed Training vs alarm -Relative risk of achieving 14 consecutive dry nights



Participants Relapsing

Participants given DBT and those given alarm treatment were equally likely to relapse (113, 114, 124). When the trials were pooled the relative risk of relapse was 1.0 (95% CI: 0.7 to 1.5) (Figure 4.5.3).

Figure 4.5.3: Dry bed Training vs alarm - Relative risk of relapsing



4.5.3 Other Multidimensional Behavioural Treatment Programme Comparisons

Two RCTs compared Dry Bed Training performed with an alarm with Dry Bed Training without an alarm (114, 124). Different Multidimensional Behavioural Treatment Programmes schedules were also compared (114, 125) as were the different elements of such programmes (123).

Table 4.5.3: Other Multidimensional Behavioural Treatment Programmes comparisons: mean number of wet nights per week and attainment of 14 consecutive dry nights

Comparison	Absolute difference in number of wet nights per week	Relative risk of attaining 14 consecutive dry nights	Relative risk of relapse
DBT: therapist at home vs therapist in hospital (Bollard, 1981A) (114A)	0.00		0.4 (0.09, 1.83)
DBT: therapist at home vs parents as therapist at home (Bollard, 1981A) (114A)	0.00		0.5 (0.10, 2.43)
DBT: therapist at hospital vs parents as therapist at home (Bollard, 1981A) (114A)	0.00		1.25 (0.39, 3.9)
DBT- office training with parent and child vs office training with parent only (Keating, 1983) (125)	0.8	0.91 (0.57, 1.44)	0.86 (0.2, 4.4)
DBT- office training with parent and child vs home training with parent and child (Keating, 1983) (125)	0.2	1.09 (0.61, 1.95)	0.7 (0.15, 3.5)
DBT- home training with parent and child vs office training with parent only (Keating, 1983) (125)	0.6	0.83 (0.48, 1.46)	1.2 (0.25, 5.7)
DBT (with alarm) vs DBT (no alarm) (Bollard, 1981B) (114B) (Bollard, 1982) (124)	 -3.79 -3.05	 4.0 (1.87, 8.55) 4.5 (1.28, 15.81)	 0.5 (0.13, 2.0) 0.3 (0.13, 0.8)

The different DBT training systems were equally likely to result in 14 consecutive dry nights and relapse.

The presence of an alarm is important. When the two studies comparing the effectiveness of DBT with and without an alarm were pooled, those utilising an alarm were 4 times more likely to achieve 14 consecutive dry nights: RR = 4.1 (95% CI: 2.2 to 7.9) (114, 124). However, when the relapse rates were pooled, those given DBT without an alarm were only 0.42 times as likely to relapse as those given DBT using an alarm: RR: 0.4 (95% CI: 0.2, 0.1).

A component analysis compared the effect of the addition of various elements of Dry Bed Training (e.g. waking, positive practice, cleanliness training) to alarm treatment. The presence or absence of these elements did not effect the number of patients attaining 14 consecutive dry nights (123).

4.5.4 Relapse Rates

Table 4.5.4 gives the relapse rates for multidimensional behavioural programmes.

Table 4.5.4 Relapse rates (%) for behavioural interventions

		3 months	6 months	12 months	12+ months
Bollard, 1982 (122)	A: DBT + alarm B: alarm	A: 6/60 (10) B: 6/35 (17)	A: 13/60 (22) B: 7/35 (20)	A: 15/60 (25) B: 10/35 (29)	A: 22/60 (37) B: 12/35 (34)
Bollard, 1982 (124)	A: DBT + alarm B: DBT C: no treatment control	A: 3/9 (33) B: 2/2 (100)			
Keating, 1983 (125)	A: DBT - office training parent + child B: DBT - home training parent + child C: DBT - office training parent only D: waiting list control	A: 2/7 (29) B: 2/5 (40) C: 2/6 (33)			

At three months relapse rates for Dry Bed Training ranged from 10 to 100% - the latter being DBT without an alarm.

4.6 Combined Psychological and Pharmacological Approaches

A summary of RCTs involving a combination of behavioural methods and drugs is given in Table 4.6

Table 4.6: RCTs with combined psychological and pharmacological approaches

Author	Number in group	Intervention
Fournier, 1987 (91)	A: 8 B: 8 C: 8 D: 8 E: 8	A: imipramine (mean dose 125 mg) B: placebo C: alarm D: random wakening E: alarm + imipramine (mean dose 125 mg)
Scholander, 1968 (118)	A: 15 B: 15	A: alarm + nortriptyline 50 mg B: alarm + placebo
Sukhai, 1989 (56)	28 crossover	A: alarm + desmopressin 20 µg B: alarm + placebo

4.6.1 Combined Approach Compared With Control

One RCT compared a combination of alarm therapy and imipramine with both placebo and random awakening (91). No measures of dispersion are given. Alarm plus imipramine resulted in 4 less nights per week (absolute difference) than placebo and 2.3 fewer wet nights per week (absolute difference) than random wakening.

4.6.2 Combined Approach Compared With Alarm

Two RCTs compared alarms augmented with drugs with other treatments (56, 91). The group receiving alarm and desmopressin had 1 less wet night per week (95% CI: -1.55, -0.45) than the group receiving alarm with a placebo (Table 4.6.1).

Table 4.6.1: Combined approach vs alarm: mean number of wet nights per week

Comparison	Difference in mean number of wet nights per week	Relative risk of 14 consecutive dry nights
alarm + desmopressin vs alarm + placebo (Sukhai, 1989) (56)	-1.0 (-1.55, -0.45)	
alarm + imipramine vs alarm + placebo (Fournier, 1987) (91)	-1.5 (absolute diff)	
alarm + nortriptyline vs alarm (Scholander, 1968) (118)		0.67 (0.27, 1.64)

There was no difference between the alarm plus amitriptyline and the alarm plus placebo groups in the numbers attaining 14 consecutive dry nights (118): RR = 0.67(95% CI: 0.27 to 1.64).

These results are based on single small trials which may have lacked sufficient power to demonstrate a difference between the conditions.

4.7 Retention Control Training

One RCT compared bladder training at camp with a no treatment control group (126) (Table 4.7).

Table 4.7: RCT involving retention control training

Author	Number in group	Intervention
Harris, 1977 (126)	A: 9 B: 9	A: bladder training at camp B: waiting list control

Those given bladder training at camp had 2.4 fewer wet nights per week (absolute difference) than controls. Retention control used as an adjunct to alarm treatment did not improve outcome (see 4.4.3).

4.8 Wakening

One RCT involved waking (91) (Table 4.8).

Table 4.8: RCT involving wakening

Author	number in group	intervention
Fournier, 1987 (91)	A: 8 B: 8 C: 8 D: 8 E: 8	A: imipramine B: placebo C: alarm D: random wakening E: alarm + imipramine

Random awakening resulted in 2.3 fewer wet nights per week (absolute difference) than placebo.

4.9 Complementary

A summary of the RCTs involving complementary approaches is given in Table 4.9.

Table 4.9a: RCTs involving complementary approaches

Author	Number in group	Intervention
Edwards, 1985 (128)	A: 12 B: 12 C: 12 D: 12	A: trance + suggestions B: suggestions C: trance D: waiting list control
Leboeuf, 1991 (127)	A: 71 B: 100	A: chiropractic B: waiting list control

The waiting list control group had 0.6 fewer wet nights per week (absolute difference) than those given chiropractic treatment (127). Various components of hypnosis were compared with control (128) (Table 4.9b).

Table 4.9b: Hypnosis vs no treatment control: Point estimate of the differences in mean number of wet nights per week

Comparison	Absolute difference in number of wet nights per week
Edwards, 1985 (128)	
trance + suggestions vs control	-1.5
suggestions vs control	-1.8
trance vs control	-2.3

4.10 Comparing Alarms and Drugs

Although six of the included RCTs contained comparisons of alarms and drugs (1, 91, 93, 100, 107, 108) only two provided the measures of dispersion necessary to calculate confidence intervals (1, 100) (Table 4.10).

Table 4.10 Comparing drugs and alarms

Comparison	Difference in number of wet nights per week
alarm vs imipramine	
Kolvin, 1972 (93)	0.0 (absolute difference)
Motavalli, 1994 (100)	-0.2 (-1.7, 1.38)
alarm vs amitriptyline	
Danquah, 1975 (107)	-0.8 (absolute difference)
Alarm vs amphetamine/ephedrine	
Wright, 1974 (108)	-2.4 (absolute difference)
Alarm vs clomipramine	
Motavalli, 1994 (100)	-1.9 (-4.18, 0.38)
alarm vs desmopressin	
week 1: Wille, 1986 (1)	+1.7 (0.45, 2.95)
week 12: Wille, 1986 (1)	-1.4 (-2.6, -0.5)

It was possible to compare desmopressin and alarm treatment in both the first and last week of treatment (1). At the end of the first week, desmopressin treatment resulted in 1.7 fewer wet nights per week than alarm treatment: WMD = 1.7 (95% CI: 0.45 to 2.96); however, in the final week (after 3 months) alarm treatment produced 1.4 fewer wet nights per week than treatment with desmopressin WMD = -1.4 (95% CI: -2.65, -0.15).

Participants receiving the alarm intervention were also 9 times less likely to relapse than those given desmopressin: RR = 9.1 (95% CI: 1.3 to 50) (1).

4.11 Adverse Events and Side Effects

Details of the side effects and adverse events reported in the included RCTs are given in Table 4.11a and 4.11b. The proportion of participants experiencing the side effects are given for each trial.

There was no reporting of side effects in 1 desmopressin trial (82); 7 imipramine trials (90, 91, 93, 95, 100, 102, 105) and three RCTs of other drugs: phenmetrazine: (112); clomipramine: (100) and amphetamine and Enuretrol: (108).

Of the desmopressin trials, 10 reported that there were no adverse effects (56, 73-75, 79, 84-88); the absence of side effects was reported in only 2 imipramine trials (94, 106) and in one trial involving two other drugs: amitriptyline and amitriptyline + desmopressin: (75).

There was no reporting of adverse events in 12 of the alarm trials (53, 91, 93, 108, 113-116, 119, 120, 122, 130); in 1 complementary trial (128) or in any of the Dry Bed Training trials (53, 113, 114, 122, 123, 125, 130); in the combined trial (91); or any of the trials of retention control training (115, 116, 126).

Of the alarm trials, 2 reported that there were no adverse reactions (107); (56).

When reported, a wide range of adverse events were detailed. Overall, trials involving desmopressin were the most likely to state that no adverse events had been found. More adverse reactions were associated with imipramine than desmopressin. Of the behavioural interventions, adverse reactions were only reported for enuresis alarms. These were most commonly complaints of alarm failure.

4.12 Costs

Enuresis places a financial burden on families. In 1985, the estimated additional cost of one child who wet the bed was £9.50 a week (Dobson, 1985, cited in (4)). Interventions vary in price (Table 4.12). Desmopressin is clearly more expensive than imipramine.

If a 16 week treatment period is considered - the usual time allowed for fourteen consecutive dry nights to be attained (68), desmopressin treatment using DDAVP (200g per night) would cost approximately £116; using imipramine hydrochloride (10 mg per night) would cost less than £1.00 and using an enuresis alarm and pad would cost approximately £40.

Table 4.11a: Details of adverse events and side effects for drugs

	Desmopressin	Imipramine	Other drugs
anorexia	1/22 (80)	1/9 (89) 2/125 (98)	
anxiety reaction		10/57 (97)	
bad taste	2/24 (1)		
burning sensation		2/25 (92)	
constipation		3/9 (89) 2/57 (97) 1/125 (98)	
depression		1/125 (98)	
diarrhoea		1/25 (98) 1/35 (103)	
dizziness		1/9 (89) 1/29 (96) 1/34 (101)	Viloxazine: 1/12 (89) oxybutynin: 1/30 (111)
drowsiness		(99) 1/35 (103)	amitriptyline: (107) chlorpotixine: (109) oxybutynin: 1/30 (111)
dry mouth		1/9 (89) 1/34 (101)	oxybutynin: 1/30 (111) nortriptyline: (118)
epistaxis	3/30 (76)		
headache	2/34 (83) 3/22 (72)	3/57 (97)	Viloxazine: 1/12 (89) desipramine: 1/53 (110) oxybutynin: 1/30 (111)
irritability		8/34 (101) 3/62 (104)	
lethargy		4/9 (89)	Viloxazine: 1/12 (89)
nasal discomfort	5/24 (1) 2/30 (76)		
nosebleeds	1/24 (1)		
postural hypotension			desipramine: 1/53 (110)
rash	1/17 (77)		
sight disturbance	1/34 (83)		
sleep disturbance		12/57 (97) 1/35 (103); 3/62 (104)	
unspecified minor	6/70 (81)A 11/51 (81)B		
upset stomach	3/22 (72)	2/9 (89) 3/29 (96) 4/57 (97)	desipramine: 3/53 (110) oxybutynin: 1/30 (111)
vomiting		2/9 (89)	

Table 4.11.b: Details of adverse events and side effects for behavioural and other interventions

	Alarms	Complementary
alarm failure	5/22 (1) 7/26 (121)	
backache		chiropractic 1/100 (127)
depression		shaming (107)
failed to wake patient	15/22 (1)	
false alarms	21/22 (1) 13/20 (117)	
fright	1/22 (1) 1/15 (118)	
headache		chiropractic1/100 (127)
loss of self esteem		shaming (107)
shame		shaming (107)
woke others	15/22 (1)	

However, such an analysis does not take account either the administrative nor the human costs involved. The Guidelines on Minimum Standards of Practice (39) suggest that follow up supervisory contacts should occur at least every three weeks, with medication reviewed at least monthly. Alarm systems may not be returned to clinics and have to be followed up. Human costs are difficult to quantify, but it is likely that alarm treatment is accompanied by broken nights for various family members until success is attained.

Table 4.12: Cost of treatment

Intervention	Net price (46)
Desmopressin DDAVP (100 g) DDAVP (200 g) Intranasal solution (100 g/mL) Desmotabs (200 g) desmospray (10 g metered spray)	 £45.95 for 90 £91.90 for 90 £9.50 for 2.5mL dropper bottle £29.00 for 28 £22.90 for 5 ml unit
Imipramine hydrochloride 10mg 25 mg Tofranil 10mg tablets Tofranil 25 mg tablets Tofranil syrup 25 mg/5ml	 £0.16 for 20 £0.10 for 20 £1.60 for 84 £3.05 for 84 £3.11 for 150 ml
Enuresis alarm and pad Replacement sensor/mat	£29.95 +VAT to £62. + VAT £12.00 + VAT to £16.50 + VAT

5 ANALYSIS OF THE ROBUSTNESS OF THE REVIEW: SENSITIVITY ANALYSIS

To be included in the main analysis, studies had to satisfy strict criteria of relevance, study design and outcome. Many of the identified studies failed to meet all these criteria. This raises the question as to whether the review would have been different if such studies were included? Do the results of these studies suggest areas where further good quality research might be worthwhile?

Three sensitivity analyses have been carried out to investigate the effects of omitting studies which are:

a) non-randomised controlled studies
b) randomised controlled trials where a systematic measurement of baseline levels of wetting has not been undertaken
c) randomised controlled trials where organic causes for wetting have not been excluded.

Non Randomised Controlled Studies

In theory, if studies are large enough, randomisation equally distributes possible confounding variables among the groups to be compared. Studies where groups are not comparable at baseline are at risk of bias due to differences in variables such as age, sex, severity of wetting and possibly unknown factors, obscuring treatment effects.

To investigate the effect of limiting the review to randomised controlled trials, the 22 studies which were not randomised but otherwise met the inclusion criteria were investigated (60, 66, 71, 131-149). Where possible, weighted mean differences and relative risks have been calculated to allow assessment of the effect of restricting the main analysis to RCTs.

Randomised Controlled Trials Where a Systematic Measurement of Baseline Levels of Wetting Has Not Been Undertaken

To be included in the main analysis, the RCTs had to include a systematic measurement of baseline wetting. This was to ensure that initial severity of wetting had been objectively measured, since parental recall of wetting levels can be misleading. In addition, some children cease to wet the bed once their wetting is actively monitored.

Twenty nine RCTs, which otherwise met the inclusion criteria, were found where the baseline levels of wetting had not been systematically measured (150-178).

These trials are discussed within a qualitative synthesis. The diversity of outcomes used renders a quantitative pooling impossible.

Randomised controlled trials where the absence of organic causes for wetting has not been established

To be included in the main analysis RCTs had to demonstrate that organic causes of bed wetting had been eliminated. Fourteen RCTs, which otherwise met the inclusion criteria, were found where this was not the case: (179-192)

A narrative synthesis only has been undertaken because the diversity of outcomes used renders a quantitative analysis inappropriate.

In addition, 11 RCTs were found which lacked both systematic baseline and exclusion of organic causes (193-203). These trials are not included in the sensitivity analysis.

Only a summary of the results will be presented here. Full details of the sensitivity analysis are given in Appendix 8.

5.1 Desmopressin

One non-randomised study compared the mean number of wet nights per week for 20 μg desmopressin and placebo (137). The mean difference was -0.4 (95%CI: -1.7 to 0.8) using the pooled estimates of standard deviation. An additional comparison of optimum dose of desmopressin was also found (149). The mean difference in the mean number of wet nights per week was -2.3 (95%CI: -3.6 to -1.0).

To assess the effect of excluding the non-randomised studies from the main analysis, the pooled random effects weighted mean differences for desmopressin were recalculated including these studies (Table 5.1). This shows that there was no appreciable change in the pooled weighted mean difference as a result of considering non RCTs.

Table 5.1: Desmopressin vs placebo: effect of including non-RCTs

Comparison	RCTs only		Including non-RCT	
	Pooled random effects WMD	Heterogeneity	Pooled random effects WMD	Heterogeneity
20μg desmopressin vs placebo	n = 519 -1.40 (-1.80, -1.01)	χ^2 = 11.72 df = 9 p>0.1	n = 563 -1.33 (-1.72, -0.94)	χ^2 = 13.8 df = 10 p >0.1
"optimum" dose desmopressin vs placebo	n = 268 -2.12 (-3.16, -1.08)	χ^2 = 7.91 df = 2 p < 0.025	n = 288 -2.15 (-2.95, -1.35)	χ^2 = 8.01 df = 3 p <0.05

5.2 Imipramine

When the three non-randomised comparisons of imipramine with placebo were pooled (using imputed standard deviations), the random effects weighted mean difference was -2.01 (95% CI: -2.79 to -1.22).

To assess the effect of excluding them from the main analyses, the non-randomised studies were entered into the pooled random effects weighted mean differences for imipramine (Table 5.2). Inclusion of the non-RCTs in the analysis does not substantially effect the pooled weighted mean difference.

Table 5.2: Imipramine vs placebo: effect of including non-RCTs

Comparison	RCTs only n = 668	Including non-RCTs n = 784
	Pooled random effects WMD	Pooled random effects WMD
Imipramine vs placebo	-1.25 (-1.73, -0.77) χ^2 = 18.76 df = 9	-1.43 (-1.89, -0.97) χ^2 = 28.41 df = 12

5.3 Other Drugs

The results for all the pharmacological studies are given in Table 5.3. The number of studies involved are given in brackets. As can be seen, in most cases the conclusion are based on just one study. It is also important to bear in mind that these studies were not included in the initial analysis because they did not meet the inclusion criteria. However, such comparison gave an indication of the robustness of the findings and of areas where good quality randomised controlled trials might be fruitful.

Table 5.3: Summary of the results of the sensitivity analysis for pharmacological interventions (number in brackets indicate the number of trials)

Intervention	Main analysis - meet ALL criteria	Including non-RCTs that meet other criteria	Including RCTs with no baseline reported	Including RCTs with medical causes not excluded
Desmopressin	superior to placebo	superior to placebo	no trials	no trials
Imipramine	superior to placebo	superior to placebo	superior to placebo	superior to placebo
amitriptyline			superior to placebo (1) inferior to imipramine (1)	
amphetamine sulphate			superior to placebo (1)	
chlordiazepoxide + amitriptyline			superior to placebo (1)	
clomipramine	similar to imipramine (1)			
desipramine	superior to placebo (1)	similar to imipramine (1)		superior to placebo (1)
diazepam			superior to placebo (1)	
diclofenac Na		superior to placebo (1)	superior to placebo (1)	
emepronium		similar to placebo (1)		similar to placebo (1)
ephedrine				similar to triclofos (1)
furosemide	similar to placebo (1)			
human chorionic gonadatrophin		ambiguous (1)		
hydroxyzine hydrochloride			similar to placebo (1)	
indomethacin			superior to placebo (1)	
meprobamate			similar to placebo (1)	
methscopolamine		inferior to imipramine (1)		
methylphenidate hydrochloride			similar to placebo (1)	
mianserin	similar to placebo (1)			
nortriptyline				superior to placebo (2)
oxybutynin	similar to placebo (1)		superior to dicyclomine	
phenmetrazine	similar to placebo (1)			
piracetam			similar to placebo (1) inferior to imipramine (1)	

pituitary snuff			superior to placebo (1)	
propantheline + phenobarbitone			similar to placebo (1)	
propantheline			similar to placebo (2)	unclear (1)
propiverin		ambiguous (2)		
trimipramine			similar to placebo (1)	
viloxazine	superior to placebo		similar to imipramine (1)	

Certain results appear to be consistent across study design and inclusion criteria. Desmopressin was found superior to placebo, regardless of design. Imipramine was also found superior to placebo regardless of whether there had been systematic measurement of baseline wetting or whether organic causes had been excluded. Desipramine was found superior to placebo not only in the single randomised controlled trial meeting all the inclusion criteria but also in one where medical reasons were not excluded. In addition desipramine was found similar to imipramine in a non-randomised trial. Two studies found diclofenac sodium superior to placebo and viloxazine was found superior to placebo in one trial which met all criteria and another which lacked baseline results.

5.4 Alarm

When the non-randomised trials were considered, those treated with alarm were 7 times more likely to attain 14 consecutive dry nights than the control group: RR: 7.07 (95% CI: 1.90 to 26.31) (133). These results were combined with those in the main analysis to see whether excluding the non-randomised studies affected the results (Table 5.4).

Table 5.4: Studies of Alarms: effect of including non-RCTs

Comparison	**RCTs only**			**Including non-RCT**		
	wet nights: WMD	Initial success: RR	Relapse: RR	wet nights: WMD	Initial success: RR	Relapse: RR
Alarm vs control		n = 177 13.32 (5.64, 31.49) χ^2 = 1.66 df = 4	n = 39 0.38 (0.20, 0.71)		n = 251 9.7 (4.73, 19.9) χ^2 = 1.91 df = 5	n = 64 0.80 (0.38, 1.68) χ^2 = 6.45 df= 1
Bed vs pants alarms		n = 40 1.00 (0.67, 1.50)		Point estimate 0.20	n = 96 0.96 (0.66, 1.41) χ^2 = 0.35 df = 1	
alarm vs alarm + desmopressin	n = 56 1.00 (1.56, 0.45)			n = 126 1.07 (0.59, 1.56) χ^2 = 0.27 df = 1	n = 71 0.61 (0.41, 0.92)	n = 43 1.27 (0.32, 4.95)

The addition of the non-randomised studies decreased the relative risk of attaining 14 consecutive dry nights with an alarm compared with no treatment from 13 to just under 10 - however, the confidence interval was considerably narrowed.

No difference was found between the bed and pants alarms in terms of attainment of 14 consecutive dry nights: RR: 0.72 (95% CI: 0.23 to 2.26). When the alarm alone was compared with the alarm plus desmopressin (131), those given the combination therapy were more likely to attain 14 consecutive dry nights: RR: 0.61 (95% CI: 0.41 to 0.92) and to have an average of 1.3 fewer wet nights per week: WMD: 1.3 (95% CI: 0.41 to 0.92). There was no difference in the relapse rate: RR: 1.27 (95% CI: 0.32 to 4.49).

When the results of these studies were pooled with those in the main analysis, it made no appreciable difference to the findings.

5.5 Multicomponent behavioural programmes

A non-randomised study found children given DBT using an alarm nearly 17 times more likely to attain 14 consecutive dry nights than the control group; RR: 16.88 (95% CI: 1.13, 251, 02). Although those given DBT with no alarm were nearly 3 times more likely to attain this than control, the confidence interval includes unity: RR: 2.7 (95% CI: 0.13 to 58.24). When the two DBT conditions are compared, those using the alarm are 9 times more likely to attain 14 consecutive dry nights: RR: 9.0 (95% CI: 1. 42 to 56.12).

Addition of the results of this study in the main analysis (Table 5.5), does not appreciably alter the findings although it does accentuate the importance of an alarm in DBT.

Table 5.5: Studies of Behavioural Programmes: effect of including non RCTs

Comparison	**RCTs only**		**Including non-RCT**	
	Initial success: RR (95% CI)		Initial success: RR (95% CI)	
DBT (alarm) vs control	n = 40	10.00 (2.69,37.24)	n = 89	11.31 (3.47, 36.87)
DBT (no alarm) vs control	n = 40	2.5 (0.13, 58.24)	n = 77	2.54 (0.65, 9.93)
DBT (alarm) vs DBT (no alarm)	n = 60	2.4 (1.02, 5.6)	n = 76	4.68 (2.53, 8.65)

5.6 Summary of Behavioural Interventions

The results of the sensitivity analysis for behavioural interventions are summarised in Table 5.6.

Table 5.6: Summary of the results of the sensitivity analysis for behavioural interventions

Intervention	Main analysis - meet ALL criteria	non-RCTs - meet criteria	RCTs - no baseline	RCTs no medical
Alarm	superior to placebo (3) superior to no treatment (3)	superior to no treatment (1)	superior to no treatment (1) louder alarm more effective (1)	superior to no treatment (4)
alarm + methedrine			similar to alarm alone (1)	
delayed alarm	similar to immediate (1)			similar to immediate (1) inferior to immediate (1)
alarm + bladder training	similar to alarm alone (3)			alarm similar to bladder training (1)
DBT (alarm)	superior to control (1) similar to alarm (4)	superior to control (2) superior to bladder training (2)		superior to control (1) similar to alarm (3)
DBT (no alarm)	inferior to DBT (alarm) (2)	superior to control (2) inferior to DBT (alarm) (1)		
3 step therapeutic programme			superior to imipramine (1)	
Full Spectrum Home Training				similar to alarm (1) less relapse than alarm (1)

Regardless of study design or inclusion criteria alarm treatment was found superior to no treatment control. Dry Bed Training was also superior to control and similar to alarm treatment. Although two non-randomised studies found that DBT without an alarm was superior to placebo, DBT without an alarm was less effective than alarm treatment alone.

5.7 Summary of Other Interventions

The results of the sensitivity analysis for other interventions are summarised in Table 5.7. Most of the interventions are subject to single studies. However, 2 studies using different designs found psychotherapy ineffective and the results of the investigations into chiropractic were mixed.

Two studies showed hypnosis to be effective, suggesting that more well designed studies could prove fruitful.

Table 5.7: Summary of the results of the sensitivity analysis for other interventions

Intervention	Main analysis - meet ALL criteria	Non-RCTs - meet criteria	RCTs - no baseline	RCTs no medical
Acupuncture		inferior to desmopressin (1)		
acupuncture + desmopressin		superior to desmopressin at 4 weeks (1)		
chiropractic	similar to control (1)	superior to control (1)		
Token economy		superior to control (1)		
cognitive behavioural		superior to control (1) similar to alarm (1)		
psychotherapy		similar to control (1)	similar to placebo (1)	
hypnosis	superior to control (1)		similar to imipramine (1)	
waking + star chart			initially superior to amitriptyline (1)	
faradization			similar to control (1)	
restricted diet			similar to control (1)	

6 DISCUSSION

It was hoped that this systematic review would provide information about the effectiveness of a wide variety of interventions used with enuresis and to a large extent it has succeeded. Only 117 of three hundred potential evaluations of the effectiveness of interventions used with enuresis were randomised controlled trials (RCTs). Of these, only 62 met the inclusion criteria of this review.

The majority of included studies are concerned with pharmacological approaches; only about one third deal with behavioural treatments. However, no RCTs meeting the inclusion criteria were found which assessed the effectiveness of star charts and rewards, fluid deprivation or lifting, all of which are commonly used interventions. In addition, no RCTs assessing psychotherapy or surgery as used with enuresis were found.

The results of any review are tempered by the quality of the included studies. This systematic review is limited to RCTs (although non-randomised controlled trials are included in the sensitivity analysis) in an effort to select the more valid studies - those where the results are more likely to reflect differences between the interventions rather than differences between the participants. In theory the presence of a control group ensures that differences are not due to external factors (for example changes with time) and randomisation of groups equally distributes any confounding variables between the groups. However, many other factors affect the quality of research and consequently the validity of findings.

Samples need to be of sufficient size for differences between groups to become statistically significant. The required sample size can be obtained using power calculations. Only two of the included randomised controlled trials included such a calculation (53, 72). In general, sample sizes were small, ranging from 2 (an alarm group) to 125 (imipramine) but on average consisted of about 22 participants. Not only can such small samples obscure treatment effects, they also make randomisation unreliable. Consequently, even though only randomised controlled trials have been included, one cannot be certain that all confounds have been eliminated.

The results of trials may be affected by how the participants were selected and by the inclusion criteria. No recruitment details are given for a third of the included randomised controlled trials (including three multi-centre trials), all of which involve drugs and have primary authors affiliated with hospital departments (56, 72-75, 80, 81, 83-85, 87, 88, 95, 96, 98, 99, 105,

110, 118). In each study stringent inclusion /exclusion criteria have been applied to ensure samples of children suffering purely from monosymptomatic nocturnal enuresis. Nine trials stated that the participants were referred directly to the trials by specialists (79, 82, 101, 103, 108, 109, 115, 116, 120). A further twelve trials involved patients attending out-patients clinics, many of which specialised in enuresis (1, 86, 89, 92, 100, 111, 113, 114, 122-124, 129). Children attending such clinics are not necessarily representative of the broader population of children who wet the bed. One trial involved a general practitioner's own patients (112). Residents in institutions for people with learning disabilities were used in 4 randomised controlled trials (94, 119), and also in a school for neglected and delinquent boys (106) and in a school for boys with hearing and speech impairment (102). Four of the randomised controlled trials used surveys of schools to locate children who wet the bed, who were then given the option of treatment (77, 93, 107, 117). Finally, participants of eight randomised controlled trials were obtained from people responding to adverts offering treatment for bed wetting (90, 91, 116, 125-129). This was the only source of participants for the two trials of complementary approaches (127, 128). People who respond to adverts are not necessarily representative of the greater population.

The clinical origins of many of the trials potentially limits the representativeness of the participants. These are people where the bed wetting has been of sufficient concern to seek professional help. However, the participants in the trials involving imipramine and those involving alarms have been recruited in a variety of ways , increasing the external validity of the studies.

Especially pertinent for enuresis are the initial severity of wetting, the possibility of an organic cause for the bed wetting and the presence of daytime wetting. To be included in this review the randomised controlled trials had to include a systematic baseline measurement of wetting and specifically exclude organic causes. Trials dealing solely with diurnal enuresis were also excluded from the review. However, only 16 randomised controlled trials explicitly excluded children who wet by day as well as night (1, 52, 56, 72, 76, 84, 86, 87, 95, 111, 113, 115, 125-128); in most, diurnal enuresis was not mentioned and 7 trials included some children who also wet by day (53, 80, 89, 104, 112, 120, 122). To have included only those randomised controlled trials which excluded all daytime wetting would have severely curtailed the scope of the review, especially as six of these dealt with desmopressin but only one with imipramine, and two each with alarm treatment and dry bed training. Consequently, considerably more of the randomised controlled trials investigating desmopressin used "pure" samples of children suffering from monosymptomatic bed wetting. Because it is likely that the underlying pathologies of monosymptomatic bed wetting and mixed night and day wetting differ, and the

former group respond better to treatment, the observed effectiveness of desmopressin may be inflated in relation to other interventions.

As mentioned above, control groups are essential when assessing the effectiveness of a treatment. The most powerful type of control is an identical placebo - and these are used in many of the drugs trials. However, a comparable no-treatment group is not so straight forward in the behavioural trials. Although a non-functioning alarm could be used, none of the trials meeting the inclusion criteria used such a device. Instead, many of the behavioural trials used a "waiting list" control group, the participants being told they would receive treatment at a later date. Clearly such an option is not equivalent to a placebo group - a completely different set of expectations will be at work, the placebo effect serving to reduce the difference between the active and control group, whereas the difference may be increased in the case of a waiting list control group. Thus it is important to take the type of control group into consideration.

Alternative interventions are also used as controls. This is the most reliable way of comparing different interventions. However, such comparisons between the most frequently used treatment modalities are rare. Only single trials were found which compared desmopressin and imipramine (77), desmopressin and alarm (1) and imipramine and alarm (103).
Although all the included trials involve a randomised, controlled design, the randomisation methods vary. Most reports merely said that randomisation had taken place, although 5 involved "true randomisation" methods including opaque envelopes (56, 74, 75, 95, 110) and another nine used methods of randomisation considered inadequate such as alternate allocation (53, 92, 96, 97, 101, 104, 113, 120, 121).

The number of participants who drop out of treatment is a significant factor when considering the effectiveness of an intervention (68). Not only does dropout rate give an indication of the acceptability of an intervention but it can influence calculations of effectiveness if results are not analysed by intention to treat. An intention to treat analysis considers all the participants who enter a trial; those who do not complete the trial are usually considered as failures, although this is not necessarily the case. If dropouts are not included, the success rate may be falsely inflated. Only eleven of the included trials were analysed by intention to treat, although another 9 stated that there were no dropouts.

The range of reported outcomes is a significant problem for enuresis research. Despite attempts to standardise outcome measures (68), these are still diverse. The majority of pharmacological research presents outcomes in terms of change in number of wet nights in a given period. Where such measures are reported in psychological reports, measures of dispersion are frequently omitted (also a problem with older drug trials). The suggested

measure: "initial success" (i.e. attainment of fourteen consecutive dry nights within a sixteen week treatment period) is rarely used in drug research, possibly because many of the randomised controlled trials have a crossover design and treatment periods of sixteen weeks are not practical within this context. Alternatively, the lack of use of "initial success" as an outcome possibly reflects differences in the aims of treatment - drugs may be seen as way to reduce the number of wet nights rather than eliminate them altogether - the latter being the aim of behavioural interventions on which the outcomes are based.

How effective are the interventions for which there is reliable evidence of effectiveness? Both imipramine and desmopressin reduced bed wetting by approximately one wet night per week as compared with placebo. In addition, people receiving either imipramine or desmopressin were approximately five times more likely than those receiving placebo to achieve fourteen consecutive dry nights. This similarity in effectiveness is borne out by the single randomised controlled trial which directly compares the two substances (77). In the longer term there is no reliable evidence that this reduction is sustained after treatment with either desmopressin or placebo ceased.

It was not possible to calculate the reduction in wet nights per week produced by alarms but those given alarm treatment were thirteen times more likely to achieve fourteen consecutive dry nights than those in no treatment control groups. Multi-dimensional behavioural treatments such as Dry Bed Training, which included the use of a alarm were also more likely to attain initial success than non-treatment control groups. Overall, no significant difference was found in the effectiveness of alarm treatment alone or multi-dimensional behavioural treatments involving alarms. Although randomised controlled trials of alarms frequently report relapse rates, these are difficult to evaluate because they depend on an initial acquisition of dryness - rarely attained by control groups. The reported relapse rates at three months ranged from 17% to 69%. However, the addition of an over learning procedure significantly reduces relapse rate (120).

These findings are supported by the results of three sensitivity analyses, which looked at the effects of contravening the inclusion criteria specifying design (e.g. randomised controlled trials); relevance (e.g. exclusion of organic factors) and outcome (e.g. baseline assessment of wetting). In addition the sensitivity analyses provided weak evidence that desipramine, diclofenac sodium and viloxazine are effective in combating bed wetting. However, in one trial the diclofenac sodium was administered as a suppository - not a treatment of choice in the UK. Hypnosis also seemed to have promising results. These interventions should be further investigated in well designed randomised controlled trials.

Thus, when comparing the relative risks of attaining 14 consecutive dry nights of pharmacological and behavioural interventions in relation to placebo, it appears that behavioral treatments are superior. This is further demonstrated in one direct comparison of the interventions (1), (although a comparison of imipramine and alarm found no significant difference (100)).

These findings are in agreement with an analysis which converted the outcomes for all groups to a common metric of the percentage of children who ceased bed wetting (70) - an approach not adopted in the present review for the sake of clarity. Children who underwent either psychological or pharmacological interventions were more likely to have ceased bed wetting by the end of treatment than were children who received placebos or no treatment. In addition, psychological treatments were generally found to be more effective than pharmacological treatments.

It should not be assumed that the interventions that are most effective in the trial situation should be the treatment of choice. A number of factors have been found to be significantly associated with failure with alarm, and similar investigations are underway for desmopressin.

A review of the factors predicting treatment outcome with an enuresis alarm analysed 6 studies employing multi variate techniques (204). Failure with the enuresis alarm was significantly associated with behavioural deviance in three studies and with family difficulties in three studies. Also significantly related were maternal education, social class, punishment, high number of baseline wet nights and multiple wet nights. These factors, however, were only indicated in one study.

A study of 43 responders and 52 non-responders to desmopressin (205) found good response to desmopressin treatment (defined as at least a 50% reduction in the number of wet nights) was related to older age, fewer initial wet nights and larger functional bladder capacity.

Professionals need to be aware of the family's understanding of and preconceived ideas about enuresis and what its treatment entails (206). Behavioural treatments involve a major investment in time and effort from the families concerned and results are not immediate. This can lead to disillusionment and possibly dropout from treatment. There needs to be good communication between professionals and families to ensure that alarms are used to their full potential.

It is essential that practitioners assess relevant family and environmental factors, child and family attitudes towards enuresis and its treatment and factors affecting treatment practicality

(39). Alarm treatment is not universally appropriate; it would be inadvisable to prescribe an alarm in a situation where there is a possibility of abuse, as a signal of bed wetting could aggravate the situation (14).

The different treatments have different financial costs. Alarm treatment involves a single outlay for the system (which if retrieved is reusable) plus the cost of sensors; the costs of drug treatment are recurrent. In addition desmopressin is considerably more expensive than imipramine.

The use of desmopressin as an adjunct to alarm treatment may be a good way of easing the initial weeks of alarm treatment (56) or for giving families a break. The rapidity of action of desmopressin over alarm was demonstrated in the direct comparison of the two (1). Desmopressin may also be useful on a "dry for camp" basis, perhaps used for specific short term reasons such as holidays or staying with friends. Some families may find desmopressin useful especially over winter to overcome laundry problems.

In summary, behavioural treatments of enuresis using alarm systems appear to be more effective than pharmacological treatments in the management of bed wetting. The associated high relapse rate can be reduced by the use of over learning procedures. Desmopressin and imipramine seem equally effective in reducing the number of wet nights but there is no reliable evidence that they have long term effects after treatment has ceased. The risks of side effects, some times fatal associated with both imipramine and desmopressin suggest that behavioural treatments are preferable to the pharmacological options.

7 IMPLICATIONS

7.1 Implications for Practice

A variety of behavioural and pharmacological interventions have been shown to be effective in combating nocturnal enuresis. However, their effectiveness is difficult to compare because of the different outcomes used. Only one reliable randomised trial directly compared treatment with an enuresis alarm to desmopressin; patients treated with the alarm were more likely to achieve initial success (1).

Treatment with an enuresis alarm is more likely to produce fourteen consecutive dry nights (initial success) than no treatment. However, the high dropout rates suggest that there are problems with compliance. Potential difficulties, such as the time needed to attain success, need to be discussed with families before embarking on this treatment. The high relapse rates can be reduced by the addition of an over-learning procedure. Multidimensional behavioural treatment programmes such as Dry Bed Training have not been shown to be more effective than alarm treatment.

Both desmopressin and imipramine rapidly reduce the number of wet nights per week as compared with placebo. However, there is no reliable information about the longer term effectiveness of these drugs. Although there appear to be fewer adverse reactions associated with desmopressin than imipramine, these are not unknown and can be fatal. Patients and their families need to be warned of the potentially lethal adverse effects of these drugs and counselled how to avoid them. Desmopressin is considerably more expensive than imipramine.

There is no evidence that the setting influences the effectiveness of treatment. The majority of the included trials have involved participants treated in their own homes. Several of the trials of multidimensional behavioural treatment programmes have found no difference in the effectiveness of Dry Bed Training when different venues were compared (114, 125). Alarm interventions have also been found to be effective in institutions such as residential children's homes (117).

7.2 Implications for Future Research

Although there has been considerable research into interventions for enuresis, much of this is of poor quality. The majority of the research included in this review has dealt with three interventions - desmopressin, imipramine and enuresis alarms. No randomised controlled trials involving systematic baseline measurements of wetting and exclusion of organic causes were

located which investigated the effectiveness of star charts and rewards, fluid deprivation or lifting - all of which are commonly used interventions. It is important to evaluate the effectiveness of these, especially as opinion of the utility of lifting varies.

The sensitivity analysis also highlights some interventions that are worthy of further research using well designed randomised controlled trials - desipramine, diclofenac sodium and viloxozine. In addition, hypnosis appears promising.

Although there are a number of evaluations of the effectiveness of desmopressin, imipramine and alarms there are few direct comparisons between treatments. Given that each has been shown to be effective, it is important to be able to draw comparisons between them.

The difficulty in comparing interventions is exacerbated by the lack of uniformity in outcome measures. Although in-roads have been made into the problem of differing outcomes used in enuresis research (68) there is still no common metric between behavioural and pharmacological approaches. It would be useful to use both numbers achieving fourteen consecutive dry nights and also average change in the number of wet or dry nights when reporting the effectiveness of treatment.

Most of the included randomised controlled trials have recruited children from enuresis clinics or are hospital based. Participating families may be especially motivated to tackle the bed wetting. In addition strict inclusion exclusion criteria have been imposed in many of the randomised controlled trials. Consequently, the children involved are not necessarily representative of the wider population of those who wet the bed. Desmopressin research in particular has been conducted using children with "monosymptomatic nocturnal enuresis". It is important to research the effectiveness of interventions on more representative samples of children.

As noted above, the use of small sample may obscure treatment effects. Many of the comparisons, especially between different types of alarms were conducted in single trials using small samples. Studies investigating the merit of e.g. supervision need to be repeated using samples whose size has been determined using power calculations.

Although not studied in the included trials, there is suggestion that not all interventions are suitable for all children. Further research is needed to determine which interventions are appropriate for which groups and why. Important factors include age, presence of daytime wetting and family circumstances.

APPENDICES

APPENDIX 1: Search Strategies

Medline search strategy

1 enuresis/
2 enuresis.tw.
3 bedwet$.tw.
4 (bed adj wet$).tw.
5 (bladder adj control).tw.
6 (dry adj day).tw.
7 (dry adj night).tw.
8 (involuntary adj3 voiding).tw.
9 (involuntary adj3 urin$).tw.
10 (involuntary adj3 micturat$).tw.
11 or/1-10
12 reward/
13 (pad$ adj bell$).tw.
14 (pad$ adj buzzer$).tw.
15 behavior-therapy/
16 alarm$.tw.
17 minialarm$.tw.
18 (mini adj alarm).tw.
19 desmopressin/
20 desmopressin.tw.
21 desmotabs.tw.
22 desmospray.tw.
23 oxybutyline.tw.
24 imipramine/
25 imipramine.tw.
26 amitryptyline/
27 amitryptyline.tw.
28 nortryptyline/
29 nortryptyline.tw.
30 psychotherapy/
31 psychotherapy.tw.
32 family therapy/
33 family therapy.tw.
34 hypnosis/
35 hypnosis.tw.
36 (bladder adj training).tw.
37 (pelvic adj floor adj exercise$).tw.
38 lifting/
39 motivation/
40 conditioning/
41 counseling/
42 overlearning/
43 diet therapy/
44 (diet adj herapy).tw.
45 (moisture adj alarm$0.tw.
46 (dry adj bed adj training).tw.
47 exp alternative medicine/
48 (alternative adj medicine0.tw.
49 acupuncture.tw.
50 homeopath$.tw.
51 chiroprac$.tw.

52 or/12-51
53 11 and 52
54 randomised controlled trial.pt
55 randomised controlled trials/
56 random allocation/
57 double-blind method/
58 single-blind method/
59 clinical trial.pt.
60 exp clinical trials/
61 (clinical$ adj5 trial$)tw.
62 (singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$0.tw.
63 placebos/
64 (placebo$ or randon$0.tw.
65 research design/
66 comparative study/
67 exp evaluation studies/
68 follow-up studies/
69 prospective studies/
70 (control$ or prospectiv$ or volunteer$).tw.
71 or/54-58
72 or/59-65
73 or/66-70
74 71 or 72 or 73
75 53 and 74
76 success.tw.
78 successful.tw.
79 effectiveness.tw.
80 76 or 77 or 78 or 79
81 53 and 80
82 75 or 81
83 from 82 keep 1-2, 5-9,11-18,21-24,26,31 33,35-36,38-40,44-45,48-55

PsycLIT Search strategy

#1: 155 ENURESIS
#2: 0 ENURESIS in DE
#3: 197 URINARY-INCONTINENCE
#4: 197 (URINARY-INCONTINENCE) in DE
#5: 11 BEDWET*
#6: 98 BLADDER
#7: 21410 CONTROL
#8: 22 BLADDER near1 CONTROL
#9: 181 DRY
#10: 8233 DAY
#11: 1 DRY near1 DAY
#12: 181 DRY
#13: 929 NIGHT
#14: 0 DRY near1 NIGHT
#15: 584 INVOLUNTARY
#16: 16 VOIDING
#17: 0 INVOLUNTARY near1 VOIDING
#18: 1110 URIN*
#19: 0 #15 near1 URIN*
#20: 3 MICTURAT*
#21: 0 #15 near1 MICTURAT*
#22: 255 #1 or #3 or #4 or #5 or #8 or #11
#23: 921 REWARDS
#24: 474 REWARDS in DE
#25: 1125 PAD*
#26: 1250 BELL*

#27: 14 BUZZER*
#28: 4 PAD* near1 (BELL* or BUZZER*)
#29: 1289 BEHAVIOR-THERAPY
#30: 1112 BEHAVIOR-THERAPY in DE
#31: 1086 BEHAVIOR-MODIFICATION
#32: 952 BEHAVIOR-MODIFICATION in DE
#33: 354 ALARM*
#34: 0 MINIALARM*
#35: 5150 MINI*
#36: 354 ALARM*
#37: 0 MINI* near1 ALARM*
#38: 6 DESMOPRESSIN
#39: 0 DESMOTABS
#40: 0 DESMOSPRAY
#41: 0 OXYBUTYLINE
#42: 2 OXYBUTYNIN
#43: 846 IMIPRAMINE
#44: 612 IMIPRAMINE in DE
#45: 11 AMITRYPTYLINE
#46: 0 AMITRYPTYLINE in DE
#47: 0 NORTRYPTYLINE
#48: 0 NORTRYPTYLINE in DE
#49: 9264 PSYCHOTHERAPY
#50: 6318 PSYCHOTHERAPY in DE
#51: 2080 FAMILY-THERAPY
#52: 1978 FAMILY-THERAPY in DE
#53: 1066 HYPNOSIS
#54: 470 HYPNOSIS in DE
#55: 588 HYPNOTHERAPY
#56: 552 HYPNOTHERAPY in DE
#57: 98 BLADDER
#58: 14221 TRAINING
#59: 6 BLADDER near1 TRAINING
#60: 0 BLADDER-TRAINING
#61: 0 BLADDER-TRAINING in DE
#62: 80 PELVIC
#63: 275 FLOOR
#64: 14221 TRAINING
#65 0 PELVIC near1 FLOOR near1 TRAINING
#66: 0 PELVIC-FLOOR-TRAINING
#67: 96 LIFTING
#68: 4810 MOTIVATION
#69: 2773 MOTIVATION in DE
#70: 8 MOTIVATION-TRAINING
#71: 8 MOTIVATION-TRAINING in DE
#72: 3766 CONDITIONING
#73: 2891 CONDITIONING in DE
#74: 7190 COUNSELING
#75: 3649 COUNSELING in DE
#76: 20 OVERLEARNING
#77: 12 OVERLEARNING in DE
#78: 875 DIETS
#79: 735 DIETS in DE
#80: 0 DIET-THERAPY
#81: 3 MOISTURE
#82: 354 ALARM*
#83: 0 MOISTURE near1 ALARM*
#84: 7 DRY near1 BED near1 TRAINING
#85: 0 DRY-BED-TRAINING
#86: 5136 ALTERNATIVE

#87: 15355 MEDICINE
#88: 17 ALTERNATIVE near1 MEDICINE
#89: 95 ACUPUNCTURE
#90: 61 ACUPUNCTURE in DE
#91: 9 HOMEOPATH*
#92: 15 CHIROPRACT*
#93: 16084 #23 or #24 or #28 or #29 or #30 or #31 or #32 or #33 or #38 or #42 or #43 or #44 or #45 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56
#94: 15624 #59 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77
#95: 1009 #78 or #79 or #84 or #88 or #89 or #90 or #91 or #92
#96: 30892 #93 or #94 or #95
#97: 103 #22 and #96
#98: 39 RANDOM-SAMPLING
#99: 37 RANDOM-SAMPLING in DE
#100: 48 EXPERIMENT-VOLUNTEERS
#101: 48 EXPERIMENT-VOLUNTEERS in DE
#102: 3095 PLACEBO
#103: 227 PLACEBO in DE
#104: 636 EXPERIMENTAL-DESIGN
#105: 636 EXPERIMENTAL-DESIGN in DE
#106: 4501 FOLLOWUP-STUDIES
#107: 4501 FOLLOWUP-STUDIES in DE
#108: 112 COHORT-ANALYSIS
#109: 112 COHORT-ANALYSIS in DE
#110: 29 RANDOMISED
#111: 4398 CONTROLLED
#112: 6534 TRIAL*
#113: 19 RANDOMISED with CONTROLLED with TRIAL*
#114: 25164 CLINICAL
#115: 1116 CLINICAL with #112
#116: 1624 DOUBLE-BLIND
#117: 99 SINGLE-BLIND
#118: 1 TRIPLE-BLIND
#119: 2250 RANDOM
#120: 669 ALLOCATION
#121: 10 RANDOM near1 ALLOCATION
#122: 604 ASSIGNMENT
#123: 80 #119 near1 ASSIGNMENT
#124: 58 EVALUATION near1 STUDIES
#125: 112 COMPARATIVE near1 STUDIES
#126: 38536 CONTROL* or PROSPECTIV* or VOLUNTEER*
#127: 8203 #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107
#128: 45220 #108 or #109 or #113 or #115 or #116 or #117 or #118 or #121 or #123 or #124 or #125 or #126 or #127
#129: 41 #97 and #128
#130: 0 #97 and #113
#131: 10600 SUCCESS*
#132: 15557 EFFECTIVE*
#133: 25073 #131 or #132
#134: 54 #133 and #97
#135: 70 #129 or #134

DHSS_DATA SEARCH STRATEGY

enuresis.de.
enuresis
bedwet$
bed adj wet$
bladder adj control

dry adj day
dry adj night
involuntary adj voiding
involuntary adj urin$
involuntary adj micturat$
or/1-10
reward
pad$ adj bell$
pad$ adj buzzer$
behavior adj therapy.de.
behavior adj therapy
behavior adj modification.de
behavior adj modification
alarm$
minialarm$
mini adj alarm$
desmopressin
desmotabs
desmospray
oxybutyline
oxybutynin
imipramine
amitryptyline
nortryptyline
psychotherapy.de.
psychotherapy
family adj therapy.de.
family adj therapy
hypnosis.de.
hypnosis
hypnotherapy.de.
hypnotherapy
bladder adj training
pelvic adj floor adj exercise$
lifting
motivation.de.
motivation
conditioning
counselling.de.
counselling
counseling
overlearning
diet adj therapy.de.
diet adj therapy
dry adj bed adj training
alternative adj medicine.de.
alternative adj medicine
acupuncture.de.
chiropractic.de.
homoeopathy.de
or/12-55
sampling adj theory.de.
clinical adj trials.de.
placebos.de.
research adj design.de.
comparative adj studies.de.
follow adj up adj studies.de.
randomised adj controlled adj trial$
randomized adj controlled adj trial$
random adj allocation

single-blind
double-blind
triple-blind
clinical adj trials
(single or double or triple or treble) and (blind$ or mask$)
comparative adj stud$
evaluation adj stud$
followup adj stud$
follow adj up adj stud$
prospective adj stud$
control$ or prospectiv$ or volunteer$
r/57-78
79 and 56
success.de.
effective.de.
success$
effective$
or/81-84
85 and 56

ASSI and AMED search strategies

enuresis
bedwet$
bed adj wet$
bladder adj control
dry adj day
dry adj night
involuntary adj voiding
involuntary adj urin$
involuntary adj micturat$
or/1-9
reward
pad$ adj bell$
pad$ adj buzzer$
behavior adj therapy
behavior adj modification
alarm$
minialarm$
mini adj alarm$
desmopressin
desmotabs
desmospray
oxybutyline
oxybutynin
imipramine
amitryptyline
nortryptyline
psychotherapy
family adj therapy
hypnosis
hypnotherapy
bladder adj training
pelvic adj floor adj exercise$
lifting
motivation
conditioning
counselling
counseling
overlearning

diet adj therapy
dry adj bed adj training
acupuncture
chiropractic
homoeopathy
or/12-43
clinical adj trials
placebos
research adj design
comparative adj studies
follow adj up adj studies
randomised adj controlled adj trial$
randomized adj controlled adj trial$
random adj allocation
single-blind
double-blind
triple-blind
clinical adj trials
(single or double or triple or treble) and (blind$ or mask$)
comparative adj stud$
evaluation adj stud$
followup adj stud$
follow adj up adj stud$
prospective adj stud$
control$ or prospectiv$ or volunteer$
r/45-64
65 and 44
success$
effective$
67 and 68
69 and 44
70 or 66

SIGLE SEARCH Strategy

SIGLE: enuresis
PROG:
TERM (ENURESIS) APPEARS IN (2) CONTEXTS
SEARCH 11 FOUND 5 ITEM(S).
SEARCH 12?
USER:
bedwet:
PROG:
TERM (BEDWET:) NOT ON INDEX
SEARCH 12?
USER:
bed adj wet:
PROG:
*NO ITEMS FOUND.
SEARCH 12?
USER:
bladder adj control
PROG:
*NO ITEMS FOUND.
SEARCH 12?
USER:
dry adj day
PROG:
*NO ITEMS FOUND.
SEARCH 12?

USER:
dry adj night
PROG:
*NO ITEMS FOUND.
SEARCH 12?
USER:
involuntary adj voiding
PROG:
*NO ITEMS FOUND.
SEARCH 12?
USER:
involuntary adj urin:
PROG:
*NO ITEMS FOUND.
SEARCH 12?
USER:
involuntary adj micturat:
PROG:
TERM (MICTURAT:) NOT ON INDEX
*NO ITEMS FOUND.

APPENDIX 2
Organisations, Manufacturers and Individuals Contacted

ERIC: The Enuresis Resource and Information Centre
The International Enuresis Research Centre, University of Aarhus, Denmark
The Continence Foundation
National Enuresis Society
The Incontinence Group of the Cochrane Collaboration
London Enuresis Clinic
ABPI (Association of British Pharmaceutical Industries)
The Alternative Medicine Group of the Cochrane Collaboration

Manufacturers of products used with enuresis

Ferrings Pharmaceuticals Ltd
Smith and Nephew Healthcare Ltd
N.H. Eastwood and Sons
Nottingham Rehab
Simcare, Eschmanm Bros and Walsh Ltd
Headingly Scientific
Astric Medical
Rhone-Poulenc Rorer Ltd
Barker-Norton Pharmaceuticals
Parke-Davis Research Laboratories
Thomas-Morson Pharmaceuticals
Approved Prescritption Services Ltd
Berk Pharmaceuticals
Cox Pharmaceuticals
Roche Products
Dista Products Ltd
CIBA Laboratories
Geigy Pharmaceuticals
Pharmica Ltd
Eli Lilly and Company Ltd
Bristol Myers Pharmaceuticals
Sanofi Winthrop Ltd
Pfizer Limited
3M Health Care Ltd
Lipha Pharmaceuticals Ltd
Wyeth Laboratories
Marion Merrell Dow Ltd
Servier Laboratories Ltd
Laboratories for Applied Biology Ltd
Wellcome Medical

Professionals involved with enuresis

Prof David Baum,
Royal Hospital for Sick Children,
Bristol

Mrs Hilary Bayliss
InconTact
Rugby

Dr R. Butler,
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Dr. A. Cisternino,
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Barnet Health Authority

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University of Bristol

Mr Peter Griffiths
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University of Sterling

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Dr John Hindemarsh
Consultant Urologist
South Cleveland Hospital

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Memphis State University, USA

Mr Stephen Hunt
Hinchingbrooke NHS Trust
Huntingdon

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Columbus , Ohio USA

Dr Victoria McGrigor
Dept of Community Child Health
Central Health Clinic
Southampton

Mr Paul McInerney
Consultant Urologist,
Deriford Hospital, Plymouth

Professor Roy Meadow
St James University Hospital
Leeds

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University of Manitoba,
Winnepeg, Canada

Dr Roger Morgan
Enuresis Treatment Service
Oxford

Mr Jens Peter Norgaard
Dept of Pediatric Surgery
Rigs Hospital
Copenhagen, Denmark

Ms Christine Norton
The Continence Foundation
London

Leon Polnay
Senior Lecturer in Paediatric Community Health
Queen's Medical Centre
Nottingham

Dr S. Rittig,
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University of Aarhus,
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Mrs June Rogers
St Helens and Knowsley Community Health (NHS) Trust
Liverpool

Dr. David Scott,
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Sweden

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Leicester

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MN. USA

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Portland,
Oregon.USA

Dr. W. Warzak
University of Nebraska Medical Center,
Nebraska, USA

APPENDIX 3: Data Extraction Form

-Ref_Number {Reference number of paper}
-Authors
-Year
-Title
-Original_Title {eg if foreign language}
-Journal_Book_Etc
-Volume
-Pages
-Country_Of_Origin
-Institutional_Affiliation
-Abstract
-MeSH
-Souces_Of_Reference {eg Medline search, mentioned in review etc}
-Title_Reviewers {Titles each checked by two reviewers}
-Get_Paper_Decision {Should the paper be obtained}
-Final_Decision {If either reviewer considers the paper relevant, it is obtained}
-Reason
-Paper_Obtained {Has the paper been obtained?}
-Type_Of_Paper {eg evaluation of treatment of enuresis, background, review}
-References_Checked {Have the references of this paper checked to ensure they do not refer to other papers of interest?}
-Prescreen {Should the paper be considered in more detail?}
-Other {eg foreign language etc}
-Prescreen_Reviewers {initials of reviewers prescreening paper}
* -Evaluation_Of_Enuresis_Treatmen {Is the paper an evaluation of a treatment for enuresis}
-Intervention_In_Each_Group {Brief details of interventions}
-Target_Population
* -Medical_Exam_Performed {Was a medical examination to rule out organic causesof enuresis mentioned in the paper?}
* -Baseline_Measure_Wetness {Was there a systematic measurement of bedwetting frequency before the intervention?}
* -Post_Treat_Measure_Wet {Was there a systematic measurement of outcome?}
* -Comparison_Group {Was there a comparison group?}
* -RCT {Was the trial a randomised controlled trial}
-Incontinence_Study {Was the study concerned with more general incontinence rather than monosymptomatic nocturnal enuresis}
-Accept_Paper {If the answer to the items marked * is YES, the paper is to be included in the review - 2 reviewers to check}
-Final_Decision {The final decision about inclusion}
-Data_Extraction_Reviewers
-Stated_Aim_Of_Study {as stated in the paper}
-Outcome {eg change in frequency of wetting, initial success etc}
-Type_Of_Treatment {eg pharmacological, psychological, unconventional}
-Details_Of_Interventions_In_Gps {A more detailed descritption of the interventions}
-Duration_Of_Treatment {How long did the treatment last - if crossover length of each treatment period}
-Setting_For_Treatment {where did the treatment take place eg home, residential instsitution}
-Describe_Supervision {What if any supervsion or guidance was given to participants in the study}
-Recruitment_Or_Sampling {How were the participants obtained?}
-Entry_Criteria_For_This_Study {What were the stated entry criteria?}
-Exclusion_Criteria_Used_Here {What were the stated inclusion criteria?}
-Details_Medical_Exam {What was involved in the medical examination?}
-Severity_Of_Enuresis {What was the wetting frequency before entry into the trial - often an inclusion criteria}
-Details_Previous_Treatment {What previous treatments for enuresis had the participants undergone?}
-Payment_Required_For_Treatment {Did the participants have to pay for treatment - rarely mentioned?}

-Number_In_Treatment_Groups {How many participants were involved in each treatment group (or overall in crossover)?}
-Sex {What was the sex distribution -by group if possible}
-Age {What was the age distribution - by group if possible}
-Class {Any socioeconomic details}
-Ethnicity {Any details on ethnic origins of participants - rarely mentioned}
-Geographic_Region {Where did the study take place}
-Other_Patient_Variables {eg family frequency of enuresis etc}
-Any_Other_Factors
-Study_Design {Was it an RCT}
-Method_Randomisation_Allocation {Any details of randomisation or allocation to groups if not RCT}
-Other_Design_Features {Was the trial blinded, a crossover etc?}
-How_Treatment_Control_Comparabl {How comparable were the treatment groups before intervention in terms ofsex, age, wetting frequency}
-Length_Baseline_Assessment
-What_Measured_At_Baseline {eg number of wet nights, size of wet patch etc}
-What_Measured_During_Treatment {as above}
-When_Measurement_Taken {Was the measurement taken during the night, in the morning etc}
-How_Was_Progress_Monitored {How were wetting incidents recorded?}
-Who_Monitored_Progress {eg parents, children etc}
-Time_Btwn_Treatmnt_And_Followup
-Other
-Number_Dropouts_During_Trtmt {How many participants failed to complete the treatment}
-How_Were_Dropouts_Handled {Were participants who dropped out included in the analysis - intention to treat}
-Number_Participants_Followed_Up
-Do_Followup_Include_Dropouts {Did analysis of followup results include those who had dropped out during treatment}
-How_Attrition_Dealt_With {{Did analysis of followup results include those who had dropped out between treatment and followup}
-Statistical_Techniques_Used
-Adjustments_For_Baseline_Diffs
-A_Priori_Estimate_Sample_Size
-Anticipated_Power_Of_Study
-What_Outcome_Measures_Used {eg change in wetting frequency, success}
-Outcome_Definitions {How were outcomes (eg success) defined?}
-Results_Baseline {eg wetting frequency before trial for each group}
-Results_Change_In_Wetness {eg wetting frequency during\at end of trial for each group}
-Results_Totally_Dry { How many participants became totally dry in each group}
-Results_Revman_Format
-Results_Relapse {How many participants relapsed during followup?}
-Results_Longterm {If treatment used longer term, what results were obtained?}
-Results_Followup {Other followup results on termination of the trial}
-Results_Side_Effects {What side effects (if any)were reported}
-Results_Patient_Preferences {What patient preferences (if any) were reported}
-Results_Compliance {What information about patient compliance (if any) was reported?}
-Results_Other
-Qualitative_Results
-Cost_Of_Interventions
-Cost_Effectiveness_Information
-Authors_Conclusion
-Reviewers_Conclusions
-Reviewers_Comments

Appendix 4: Details of Studies Included in the Review

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(74) Birkasova, 1978 Czechoslovakia	A: 10 µg DDAVP drops intranasally at bedtime B: 40 µg DDAVP drops intranasally at bedtime C: placebo Duration of treatment: 2 weeks in each group	Number of subjects: 22 14 boys Mean age 6.6 yrs (range 4 to 12) Previous treatment: All had failed to respond to psychotherapy and a regimen that included fluid deprivation after 5pm. Some had previously been unsuccessfully treated with imipramine Baseline wetting: mean (sd) wet beds per fortnight = 10.6 (4.9)	Randomised crossover trial Follow-up after 4 to 6 weeks Exclusion criteria: organic causes of enuresis	Mean (sd) number of wet nights per fortnight A+ B: 4.2 (4.5) C: 11 (4.4) 5 patients receiving higher dosage totally dry 9 continued DDAVP single blind for 4-6 weeks then given placebo. 7 remained dry without drug; 1 wet once monthly and 1 returned to daily wetting. 4 who had wet nightly continued on DDAVP for 3 more months by which time 2 dry, 1 had wet night per fortnight and 1 had one wet night in 3 2 patients who were indifferent to wetting showed no response to desmopressin or placebo	1) No details of daytime wetting 2) No measure of comparability at baseline 3) No washout period 4) Not clear if intention to treat -no details of dropouts 5) Subjects are very young 6) High and low doses combined in analysis

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(88) Tuvemo, 1978 Sweden	A: 20 µg intranasal DDAVP (Minirin) just before bedtime after emptying bladder B: identical placebo as above Duration of treatment: 28 days in each group	Number of subjects: 18 Age range 6 to 12 yrs Previous treatment: Children had not responded satisfactorily to previous treatment with imipramine or amitriptyline Baseline wetting: mean (sem) number of DRY nights out of 28 = 7.5 (2.98)	Double blind, randomised crossover No follow-up Inclusion criterion: Age at least 6	Mean (sem) number of dry nights out of 28 A: 21.7 (1.72) B: 12.1 (2.07) No physical or subjective side effects observed Number of children whose results were said to be excellent: 8 relatively good: 8 unsatisfactory: 2	1) No details of daytime wetting 2) Not stated if comparable groups 3) No washout 4) No details of dropouts; unclear if intention to treat 5) No follow-up 6) Active and placebo results combined so cannot see any order or carryover effects
(85) Segni, 1982 Italy	A: 20 to 30 µg Desmopressin B: placebo Duration of treatment: 1 week	Number of subjects: A: 20 B: 20 Dropouts: A: 0 B: 12? Boys: A: 14 B: 10 Age 4 to 15 yrs with persistent enuresis mean: 8.59 yrs Baseline wetting: A: 5.2 B: 4.6	Randomised controlled trial Inclusion criteria: age 4 - 15 years; constant enuresis; no physical deformity or neurological damage Dropouts included in analysis Followed up after 1 week	From graph: mean number of wet nights per week A: 2.2 (0.3) B: 4.2 (0.4) No cases of total dryness No side effects	1) Italian language 2) No details of daytime wetting 3) Not reported if comparable groups 4) Comparison with placebo for one week only 5) Results taken from graph 6) Follow-up for 1 week only 7) No details previous treatment

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(73) Aladjem, 1982 Israel	A: 10 µg DDAVP intranasally B: placebo as above Duration of treatment: 30 days	Number of subjects: A: 15 B: 17 Number of boys: A: 7 B: 8 Mean age: A: 10.5 yrs B: 10.0 yrs (range 7 to 15) Previous treatment:5/ 23 responded to chlorimipramine hydrochloride Baseline wetting: mean (sd) number of wet nights in 30: A: 18.7 (6.5) B: 21.3 (8.5)	Double blind, randomised controlled trial No sig diff between groups in urine osmolalities Follow-up after 30 days	Mean (sd) number of wet nights out of 30: A: 6.5 (9.2) B: 18.8 (8.3) Number totally dry: A: 6 B: 1 Number of wet nights at Follow-up: A: 15.7 (8.9) B: 16.9 (9.4) Sig diff in response of children according to age. Only those over 10 yrs became completely dry. The only failures (n = 3) were less than 10 yrs old No side effects reported Prompt response to DDAVP - as early as 1-3 days	1) No details of diurnal wetting 2) Unclear about dropouts 3) Short Follow-up 4) Age effect noted. 5) Entry \ inclusion criteria not stated

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(82)A Post, 1983 A USA	A: 40 µg Desmopressin intranasally at bedtime B: placebo Drinking prohibited until the next morning Duration of treatment: 2 weeks each group	Number of subjects: 52 40 boys Mean age: 9.0 yrs Previous treatment: 18 had previous pharmacologic treatment; 3 had undergone urethral dilation procedures and 16 subjects had been involved in identical study of lower dose (20mcg) of desmopressin Baseline wetting: Mean (sem) number of dry nights = 2.52 (0.28)	Multi-centre, double-blind, randomised crossover trial Inclusion criteria: healthy children; age 6 to 16; history of severe primary or secondary enuresis Exclusion criteria: organic causes Follow-up after 1 to 3 months	Mean (sem) number of dry nights per 14 A: 6.23 (0.65) B: 4.00 (0.53) No sig order effects. Post treatment results - mean number of dry nights per 14 = 3.44 (0.50). Only 4 of 21 responders reported persistent effect. During longer term study of nine patients at Syracuse, the mean number of dry nights while taking desmopressin = 5.11 (1.31) was the same as that during the two week treatment period = 5.11 (1.59) No side effects reported.	1) No details of medical 2) No details of diurnal wetting 3) Not stated if comparable groups 4) No washout 5) No details of dropouts - unclear if intention to treat 6) Results from 3 centres combined because no sig diff in mean number of wet nights during active treatment
(82)B Post, 1983 B USA	A: 20 µg Desmopressin intranasally at 8..00pm each night B: placebo Drinking prohibited until the next morning Duration of treatment: 2 weeks each group	Number of subjects: 20 15 boys Mean age: 8.9 yrs Previous treatment: as Post 1983A Baseline wetting: mean (sem) number of dry nights = 1.90 (0.43)	Multi-centre, double-blind randomised crossover trial See (82)A	Mean (sem) number of dry nights per 14: A: 4.25 (0.88) B: 2.35 (0.51) Post-treatment mean no. dry nights per 14 = 4.00 (0.66) Comparing the results of 16 children who had both low and high dose (Post 1983A), they did better on high dose - mean paired increase = 2.18 (0.90) t = 2.44 p<0.05). Six children had increase of 3 or more dry nights while on higher dose	See (82)A

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(79) Kjoller, 1984 Denmark (207)	A: 10 µg DDAVP intranasally before bedtime B: 20 µg DDAVP intranasally before bedtime C: placebo Duration of treatment: 1 month	Number of subjects: A: 13 B: 12 C: 12 Mean age: 11.0 yrs (range: 9 to 15) Previous treatment: All failed treatment with tricyclic antidepressants and\or enuresis alarm Baseline wetting: mean (se) number of wet nights per 100 A: 56.6 (8.0) B: 65.9 (7.5) C: 64.7 (7.3)	Double-blind randomised controlled trial Entry criteria: normal, healthy children who had failed previous treatment Informed consent; More than 25% wet nights during baseline Follow-up after 3 months	Mean (se) number of wet nights per 100: A: 35.5 (10) B: 35.0 (7.6) C: 54.8 (8.8) Follow-up: mean (se) number of wet nights per 100 nights: A: 60.9 (11.4) B: 60.0 (8.5) C: 52.3 (8.9) No side effects observed Desmopressin ineffective when participants had respiratory tract infections	1) No details for diurnal wetting 2) Not reported if comparable groups 3) No dropouts reported 4) Dropouts from follow-up A: 3 B: 2
(86) Terho, 1984 Finland	A: 20 µg DDAVP intranasal drops B: placebo Duration of treatment: 2 periods of 3 weeks in each group	54 children but 5 children excluded Age range: 7 to 16 yrs Previous treatment: 49 had awakening protocol: 46 had water deprivation; 43 had tricyclic antidepressants; 13 had psychological counseling; 2 had alarm device; 1 had no previous treatment. Baseline wetting: no details	Double blind, randomised, cross over 2 periods of DDAVP and 2 periods on placebo, each period lasting 3 weeks and mutual order of all 4 periods being selected randomly Exclusion criteria: faecal soiling; voiding difficulties; obvious neurological abnormalities; diurnal wetting 5 children excluded from analysis because of error in medication Follow-up after 4 weeks	Mean % (sd) number of WET nights during combined periods: A: 30.9 (28.7) B: 57.5 (26.1) Only 1 child remained dry during follow-up period	1) Not reported if comparable groups 2) No washout 3) Unclear if intention to treat 4) Baseline and follow-up results lumped together 5) 5 excluded because of error in medication 6) Short follow-up

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(76) Fjellestad-Paulsen, 1987 Sweden	A: 200 µg oral desmopressin B: 20 µg intranasal desmopressin C: placebo tablets D: placebo nasal pipette Duration of treatment: 2 weeks placebo then 2 weeks each group	Number of subjects: 30 1 dropout 20 boys Mean (sd) age: 9.8 yrs (2.5) (range 6 to 15) Previous treatment: 69% tried one or more other treatment Baseline wetting: mean no dry nights in week = 2.2 (0.2)	Randomised double blind, double dummy, cross over trial. Periods of treatment preceded and followed by one week of observation. Exclusion: urinary tract infections; diurnal wetting; faecal soiling, neurological or urological abnormalities; 3+ wet nights a week during baseline Follow-up after 1 week	During treatments mean number of dry nights A: 4 B: 4.1 C: 2.5 2 patients totally dry while taking tablets; 1 patient totally dry while using intranasal 9 children (31%) remained totally dry No significant adverse effects but 2 patients complained of occasional nasal discomfort and 3 of epistaxis but no diff between placebo and active	1) Not reported if comparable groups 2) No washout 3) Not intention to treat 4) Many results only given graphically 5) Short follow-up
(83) Rittig, 1988 Denmark	Dose titration period then A: optimum dose of desmopressin B: placebo (3 weeks blindly inserted into 24 week treatment period) Duration of treatment: 24 weeks	Number of subjects: 34 12 boys & 11 girls; 8 women & 3 men Age: children mean 13yrs (range 8 to 17); adults mean: 25 yrs (range 18 to 45) Previous treatment: All failed previous treatments including alarms and\or tricyclics Baseline wetting: At least 3 wet nights per week.	Double blind, randomised crossover design. Placebo period of 3 weeks randomly and blindly placed through out treatment period Only patients who responded in dose titration period entered into randomised trial. Daytime wetting: excluded Six non responders not entered into crossover trial. All children (4 girls and 2 boys)	Mean number of dry nights per week A: 7 B: 4	1) Only patients who responded to desmopressin included 2) Children and adults analysed together 3) Placebo period not equal to active drug period. 4) No washout period

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(81) Miller, 1990 USA (208); Beselaar Associates protocols GHBA-351 and GHBA-352	A: 20 µg desmopressin acetate intranasally at bedtime B: 40 µg desmopressin acetate intranasally at bedtime C: placebo as above Duration of treatment: 4 weeks	Initially 180 participants. Details of 176:1A: 32 1B: 36 1C: 31 2A: 27 2B: 24 2C: 26 4 dropouts 79% boys Age range 7 to 14 yrs (46% aged 7 to 8) Previous treatment: 58% taken other drugs: 87% imipramine. 40% tried other measures - of these 76% tried enuresis alarm Baseline wetting: mean number of wet nights in 14: Centre 1: A: 12.3 B: 11.8 C: 12.3 Centre 2: A: 12.6 B: 12.3 C: 12.4	Multi-centre, double blind randomised, controlled trial. No sig differences between groups except that more older children in 20mcg in one centre 4 weeks open label phase then 2 week no treatment Entry criteria: children aged 7 to 14 with nocturnal enuresis; informed consent from parents; ten or more wet nights per fortnight; no organic urologic disorders; no urinary tract infection; no abnormal urine osmolality Number at 2 week follow-up: 1A: 19 1B: 26 1C: 16 2A: 19 2B: 20 2C: 20	Mean number of wet nights in final 14 days Centre 1: A: 8.7 B: 7.0 C: 10.7 Centre 2: A: 10.0 B: 8.1 C: 10.5 In both, active sig diff from placebo with exception of Centre 2 AvsC NS 2 week follow-up: mean number of wet nights per 14 Centre 1: A: 11.1 B: 11.0 C: 9.9 Centre 2: A: 10.8 B: 11.4 C: 11.3 No serious adverse events in either study	1) No details of diurnal wetting 2) Not intention to treat 3) Short follow-up 4) Stats suggest sample size too small for conclusive findings

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(72) Janknegt, 1990 The Netherlands	A: placebo nasal pipette B: 20 µg desmopressin intranasally C: 40 µg desmopressin intranasally Duration of treatment: 1 month each condition	22 participants: no dropouts 18 boys Mean age: 10 yrs (range: 6 to 16) Previous treatment: all used imipramine\ other medications. Also enuresis alarm (8); acupuncture (1); psychotherapy (1). More than one method used with many patients. Baseline wetting: mean (sd) number of DRY nights per week: 1.3 (1.3)	Double-blind randomised crossover of dosages with placebo between. Entry criteria: max 4 dry nights a week during baseline; Follow-up after 4 weeks	Mean (sd) number of DRY nights per week: A: 1.7 (1.8) B: 3.6 (2.5) C: 3.2 (2.2) At follow-up mean (sd) number of dry nights per week = 2.2 (1.8) Morning urine osmolarity not sig diff in pre-treatment or treatment periods Sig increase in body weight. No sig changes in blood pressure, haematology or blood chemistry. Commonest adverse reactions were headaches and stomach ache (though no diff from placebo)	1) Not reported if comparable groups 2) Cannot analyse crossover for order effects 3) Power calculation = 80%
(87) Terho, 1991 Finland	A: intranasal desmopressin (20 µg) at bedtime rising to 40 µg if no response B: placebo Duration of treatment: 2 periods of 3 weeks in each condition	52 participants: no dropouts 35 boys Age range: 5 to 13 yrs Previous treatment: 52 had night awakening; 52 had fluid restriction; 29 had used tricyclic antidepressants; 25 had used enuresis alarm Baseline wetting: mean (sd) number of DRY nights per week = 0.6 (0.2)	Double-blind, randomised crossover. Children allocated to 2 periods of desmopressin and 2 periods of placebo. Each period lasted for 3 weeks and mutual order of all 4 periods selected at random. Closed by 3 week observation period. Entry criteria: lifelong nocturnal enuresis; no diurnal wetting; no soiling; no urological or renal pathological conditions Follow-up after 3 week	Mean (sd) number of dry nights per week: Period 1: A: 4.4 B: 2.1 Period 2: A: 4.6 B: 2.5 15 children became totally dry during desmopressin treatment. 5 patients remained dry after treatment 47 patients relapsed after treatment	1) Not reported if comparable groups 2) No washout reported 3) Short follow-up

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(80) Martin Hernandez, 1993 Spain	A: placebo B: 40 µg Desmopressin drops 15 mins before retiring Duration of treatment: 2 months	Subjects: A: 22 B: 22 Boys A: 54% B: 41% Mean age: A: 8.9 yrs B: 9.13 yrs Previous treatment: all children had failed to improve during 1 month treatment with motivational therapy and bladder training Baseline wetting: mean (sd) % of dry nights per month: A: 24.45 (18.8) B: 19.9 (20)	Double-blind, randomised, placebo controlled trial Groups similar at baseline Only 7 desmopressin success followed up	Mean (sd) % of dry nights per month after 2 months A: 47.4 (32.1) B: 69.2 (33.5) Number (%) children becoming totally dry A: 1 (5) B: 5 (27)	1) Daytime wetting not excluded 2) No follow-up 3) Very small sample 4) Unclear about dropouts 5) Inclusion\ exclusion criteria not stated

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(84) Rushton, 1995 USA	A: 20 µg desmopressin spray, dose doubled if not completely dry after 14 days B: placebo as above Duration of treatment: 4 weeks	Number of subjects: A: 49 B: 47: no dropouts reported 71 boys mean age: 9.7 yrs (range: 7 to 14) Severity: mean number of wet nights during 2 week baseline: A: 11.16 (2.44) B: 10.96 (2.53) No sig. diff. between the groups in demographics. Follow-up after 5 months	Double-blind, multi-institutional, randomised controlled trial. Entry criteria: Confirmed monosymptomatic nocturnal enuresis; wet 6+ nights during 14 day baseline; no organic urological disease; no daytime wetting; no central diabetes insipidus; no urinary tract infection in previous 18 months; no use of any drug that could affect urine concentration; no medical treatment for hyperactivity or attention deficit disorder; no history of acute or perennial rhinitis, rhinorrhea or nasal polyps; no clinically significant medical disease that may interfere with the study	Mean number of wet nights (sd) Period 1 (20 mcg) A: 7.91 (4.74) B: 9.79 (3.28) p = 0.026 Mean number of wet nights (sd) Period 2 (40 mcg) A: 7.54 (5.04) B: 9.79 (3.63) p = 0.014 No adverse experiences noted No meaningful differences between responders and non-responders with regard to demographic variables of age, sex race or family history	1) No follow-up results 2) No details of previous treatment
(78) Janknegt, 1997	A: 200µg desmopressin tablets A: 400µg desmopressin tablets Duration of treatment 4 weeks	Number of subjects: A: 34 B: 31. 3 dropouts Boys: A: 18 B: 19 Mean age 19.4 yrs (range 12 to 45) At least 6 wet nights in 2 week baseline 12 week open label follow-up	Double blind multicentre randomised controlled trial. Exclusion criteria: diurnal wetting; other medical conditions; urological causes of wetting	Mean change from baseline wetting (wet nights per week 995% CI) A: -3.2 (2.4, 4.1) B: -3.4 (2.7, 4.1)	1) Only desmopressin responders 2) Mixed age

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(75) Burke, 1995 Australia	A: Amitriptyline hydrochloride (25 mg or 50 mg) B: desmopressin (20 µg) C: desmopressin + amitriptyline Duration of treatment: 16 weeks	Number of subjects: A: 14 B: 17 C: 14 Dropouts A: 0 B: 3 C: 3 Boys: A: 11 B: 10 C: 9 Mean (sd) age: A: 8.6 yrs (2.4) B: 8.9 yrs (2.5) C: 8.9 yrs (2.4) (range 6 to 14) Baseline wetting: mean (sd) number of wet nights per week A: 5.8 (0.9) B: 6.0 (0.9) C: 6.3 (0.9) No sig difference between groups in terms of number, age, height and weight	Multi-centre, double-blind randomised controlled trial. Trial prematurely halted due to one drug ceasing to be available. Entry critera: aged 6 to 17 years; wet at least 3 wet nights per week for preceding 3 month period and not dry for more than 6 months; no enuresis treatment in preceding 6 months; no nocturnal enuresis of neurogenic origin; no urinary tract infection; no abnormal urinalysis haematology or blood biochemistry; no concomitant medication known to interfere with study medication Follow-up after 12 weeks	Mean (sd) number of wet nights per week A: 3.3 (1.9) B: 4.7 (1.7) C: 3.3 (2.5) Number attaining cure A: 3 B:1 C: 5 7 out of 8 children who were cured relapsed. The exception was treated with amitriptyline+desmopressin Follow-up Mean (sd) number of wet nights per week A: (n = 10) 3.9 (2.9)) B: (n = 5) 3.8 (1.9) C: (n = 8) 5.1 (3.2) No sig side effects reported Most parents said all the drugs easy to use	1) Not stated if intention to treat 2) Not full quota of subjects 3) No details of daytime wetting

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(1) (209) Wille, 1986 Sweden	A: intranasal desmopressin (20 µg) B: Enuresis alarm Duration of treatment: 3 months	Number of subjects: A: 25 B: 25 Boys and girls Age: over 6 yrs Baseline wetting: mean number of DRY nights per week: A: 2.1 B: 1.9 Number completing treatment: A: 24 B: 22	Randomised controlled trial. Distribution of social class of parents in two groups was similar Entry criteria: age over 6 years; not dry for more than 6 months; at least 3 wet nights per week at baseline; written informed parental consent; no treatment for enuresis during previous year; no daytime wetting; no cardiovascular disease; no renal disorder; no neurological disease; no urinary tract infection Dropouts not included in analysis	Mean (sem) number of DRY nights per week in first week: A: 4.2 (0.5) B: 2.5 (0.4) In last week of treatment: A: 4.9 (0.5) B: 6.3 (0.4) A: 10 relapses given 3 months more treatment. Successful for 7/10 but 4/7 relapsed immediately and 1/7 after 2 months. B: 1 relapsed and further treatment unsuccessful. Side effects: A: nasal discomfort (5); bad taste in throat (2) B: false alarms (21); alarm did not go off (5); alarm did not wake child (15); other family members woken (15); child frightened by alarm (1). LAB TESTS: urine osmolality and density higher during treatment with desmopressin and urine osmolality in alarm group lower during treatment than before.	1) Direct comparison of desmopressin and alarm 2) Not intention to treat analysis 3) Results taken from graphs

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(77) Holt, 1986 Norway	A: imipramine 50mg and placebo nasal spray B: intranasal desmopressin 20 µg and placebo tablets Duration of treatment: 4 weeks	Number of subjects A: 19 B: 17 Mean age A: 9.8 yrs B: 9.5 yrs (range 8 to 12) Baseline wetting: wet bed 2 or more times a week	Double-blind randomised controlled trial Entry criteria: 2 or more wet nights per week; age 8 to 12; no day time wetting; no diabetes insipidus or other chronic illness where need daily medication; no other treatment for bed wetting Comparable in terms of sex, age, weight Follow-up after 6 weeks	Results first 2 weeks of treatment - % reduction in wet nights A: 48% B: 45% Results final 2 weeks of treatment: A: 54% B: 32%. Mean (sd) number of wet nights per first 14 days A: 4.9 (4.3) B: 4.8 (4.0) Mean (sd) number of wet nights per last 14 days: A: 4.5 (3.7) B: 6.0 (4.4) Mean (sd) number of wet nights per 14 days at follow-up A: 7.7 (3.9) B: 7.3 (4.5)	1) Norwegian translation 2) Direct comparison of imipramine and desmopressin 3) No details of previous treatment

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(101) Poussaint, 1965 USA	A: Imipramine (4 weeks) then placebo (4 weeks) B: placebo (4 weeks) then imipramine (4 weeks) C: Imipramine (4 weeks) then imipramine (4 weeks) D: placebo (weeks) then placebo (4 weeks) Duration of treatment: 4 or 8 weeks	Number of subjects A: 13 B: 13 C: 10 D: 11 7 dropouts 36 boys Age range 5 to 16 yrs Previous treatment: 2 children had psychotherapy for at least a year Baseline wetting: average number of wet nights per week: A: 5.2 B: 5.9 C: 5.7 D: 5.6	Double-blind -crossover in some cases. Assigned to treatment in rotation Entry criteria: high frequency enuresis - more than one wet per week Follow-up after 2 months	In crossover trial drug better than placebo in 69%, equal in 23% and placebo better than drug in 8% In non-crossover, average number of wet nights in final week of treatment C: 2.4 D: 4.2 Number of children totally dry C: 6 D: 1. No relapses Only relapses were when medication abruptly withdrawn - all had medication restored 8 children more irratable. Other complaints: dizziness (1), dry mouth (1), decreased appetite (1). Similar complaints noted in placebo children	1) Urinalysis by own physician 2) Dubious baseline 3) No details of daytime wetting 4) Not stated if comparable groups 5) No washout phase 6) Not intention to treat 7) Short follow-up 8) In follow-up 24% of children "cured" by imipramine 9) Results from graphs
(96) Manhas, 1967 India	A: Imipramine (25 mg for under 12 and 50mg for over 12) B: placebo C: placebo then imipramine D: imipramine then placebo Duration of treatment: 4 weeks each group	Number of subjects: A: 29 B: 27 C: 8 D: 8 31 boys Age range 5 to 15 yrs Previous treatment: no details Severity: regular and consistent bed wetters	Double-blind CCT (alternate allocation). Part crossover	Number attaining complete relief A: 19 B: 1 Part relief A: 6 B: 3 No relief A: 4 B: 23 3 cases of abdominal pain; 3 cases of giddiness (one with placebo); one case of dryness of mouth, headache, abdominal pain and epistaxis	1) No baseline results 2) No details of diurnal wetting 3) Comparability of groups not reported 4) No details of dropout 5) No follow-up 6) No details of inclusion\exclusion criteria

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(106) Thomsen, 1967 USA	A: imipramine (25 mg for under 12 yrs old; 50 mg for over 12yrs) B: placebo Duration of treatment: 4 weeks in each group	Number of subjects: initially 30 boys: 11 dropouts Setting: Residential homes for dependent, delinquent and neglected boys Mean age 12 yrs (range 7 to 16) Previous treatment: reduction of fluid intake and getting up during the night Baseline wetting: mean number of wet nights per two week = 9.8	Double blind, randomised crossover then both groups taking active drug after control period Entry criteria: Wetting beds regularly (at least twice a week) Follow-up after 4 weeks	Results of only one treatment regimen given but numbers look as though both groups combined	1) Outcomes not clearly defined 2) No details of daytime wetting 3) Comparability of groups not reported 4) No washout 5) Not intention to treat 6) Short follow-up 7) Institutional setting 8) Placebo not used in analysis 9) All boys

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(104) Shaffer, 1968 UK	A: high dose imipramine (75 mg) B: low dose imipramine (50mg) C: placebo Duration of treatment: 1 month each group then each group split in two - half had treatment abruptly stopped, half had treatment reduced over 4 weeks	81 participants: but 14 excluded because of urinary infection or improvement before treatment and 5 others stopped attending before treatment started. Of 62 who entered trial 3 gave no results 49 boys 40 children aged less than 8 yrs 29 day wetters No previous treatment: Severity: Wetting at least twice a week. 30 said to have had a month of consecutive wet nights and in preceding month only 7 said to have had 14+ dry nights.	Double blind, double-crossover with stratified randomisation consisting of sets of Latin Squares, catering for age, sex and previous psychiatric treatment. Allocation to abrupt vs gradual withdrawal also by random plan. Entry criteria: Any child of school age with a history of nocturnal enuresis more than twice a week provisionally accepted. a) investigations revealed no disease or abnormality b) wetting 3+ times a fortnight No significant differences between groups	Of 17 subjects, 15 showed appropriate rise and fall of dry nights with drug. No stats. (NB why not 28 subjects) Within subjects comparing doses no evidence that any diff between high and low (looking at patterns for 11 subjects (why not 18) Between subjects - significant differences found between conditions only in period 4 for placebo and low and placebo and high. 3 became restless and irritable, tearful and fidgety, difficulty in concentrating. Sleep disturbances found in 6. Those showing behaviour disturbances all considered disturbed before - treatment appeared to exacerbate symptoms.	1) Daytime wetting not excluded 2) No washout 3) Not intention to treat analysis 4) Urine examination was abnormal in 21 children 5) 11 children had associated faecal soiling 6) No raw data 7) Some groups inexplicably not included in analysis

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(92) Ingle, 1968 India	A: tranquillisers - meprobamate (400 mg daily and hydroxyzine 1mg kg daily) B: Imipramine - 25 mg daily increased to 50 mg in some cases Duration of treatment: 6 weeks	Number of subjects: A: 13 B: 12 Boys A: 6 B: 5 Mean age A: 8.9 yrs B: 8 yrs Most had previous treatment from other practitioner without any relief Baseline wetting: mean frequency of wetting A: 8.8 B: 9	Alternate allocation to groups Age, sex distribution and frequency of bed wetting comparable in groups Entry criteria: wetting consistently over 3 years Follow-up after 1 week	Mean (sd) frequency of wetting: A: 6.5 (1.19) B: 1.9 (2.11) Number totally dry (not defined) A: 0 B: 5 (2 in A showed some improvement) Nearly 60% who responded relapsed after discontinuation of the drug When tranquilliser group given imipramine 5 became totally dry and 6 showed improvement 2 complained of burning sensation	1) No details of daytime wetting 2) No details of blinding 3) No details of dropouts 4) Very short follow-up 5) No statistical analysis 6) No details how progress monitored or when measurements taken
(90) Bindelglas, 1968 USA	A: imipramine (25 mg for 11yrs and under, 50 mg for those over 11) B: placebo Duration of treatment: 1 month	Number of subjects: 63 studied over 16 month Boys: 59 Mean age: 11.5 yrs Baseline wetting: unclear	Double-blind randomised, controlled trial All patients given drug after 1 month then followed up for up to 24 months	No significant difference was found between placebo and baseline Drug performed significantly better than placebo or baseline	1) No details of daytime wetting 2) Not reported if comparable groups 3) No details for dropouts 4) No explicit entry criteria 5) No details previous treatment

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(95) Kunin, 1970 USA	A: imipramine hydrochloride (25 or 50 mg) B: ephedrine sulphate (7.5 or 15mg) Duration of treatment: 28 days in each group	NB GP A only 18 participants 8 boys Mean age: 7.7 yrs (range: 5 to 11 yrs) Severity at baseline: mean number of WET night over 28 days: 19.8	Double-blind, randomised, crossover with 1 week washout. Entry criteria: average of 3 wet nights per week; no diurnal wetting Follow-up: length not specified	Mean number of wet nights over 28 days: A: 9.2 B: 17.4 5 children became completely dry but all required medication. Eight children were dry 90+% of the time with 2 children needing no further medication	1) Unclear if intention to treat 2) Only part of trial with no organic origin included here 3) No details of previous treatment 4) No details daytime wetting
(102) Roy, 1970 France	A: 25 mg imipramine B: corresponding placebo C: no treatment control Duration of treatment: 7 weeks	Deaf and dumb boys attending a specialised boarding school Number of subjects: A: 14 B: 6 C: 6 mean age 11.4 yrs (range 7 to 17) Baseline wetting: mean number of wet nights per week: A: 4.2 B: 3.1 C: 2.5	Randomised controlled trial Groups comparable in age but significant difference between groups in terms of baseline wetness Entry criteria: age 6+; normal urinalysis; wetting bed 1+ times a week; no other medication Follow-up after 2 weeks	Mean number of wet nights per week A: 1.8 B: 2.0 C: 2.6 Adjusted means A: 1.6 B: 3.2 C: 2.9 Three psycho social factors had a significant negative correlation with percentage improvement: age of child; number of years resident in the institution and depression score	1) Foreign language 2) Sketchy medical 3) No details daytime wetting 4) Not comparable groups 5) Not stated if intention to treat 6) No details previous treatment

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(97) Martin, 1971 USA	A: imipramine pamoate 10mg (suspension) B: imipramine pamoate 25mg (suspension) C: placebo given orally one hour before bedtime Duration of treatment: 26 days in each condition	57 participants: no dropouts 42 male Age range 5 to 15 yrs Baseline wetting: mean number of WET nights in 26: 20.7	Double-blind, randomised crossover. Exclusion criteria: Organic heart disease; hyperthyroid; glaucoma; diabetes; kidney or liver disease; those taking thyroid, MAO inhibitors or anticholinergic Must have 3 nights per week for a period of more than six months Follow-up after 3 months	Mean (sd) number of wet nights in 26 days: A: 13.7 (4.12) B: 10.5 (6.03) C: 16.8 (6.49) Reported side effects: Anxiety reaction; Constipation; sleep disturbance; abdominal pain; headache; weight loss	1) No details of daytime wetting 2) Comparability of groups not reported 3) No washout 4) No details previous treatment
(103) Schroder, 1971 Germany	A: imipramine 30 mg twice a day B: placebo Duration of treatment: 25 days	Originally 96 subjects. Results from A: 35 B: 27 Age 3.5 to 11 yrs Previous treatment: had various different treatments Baseline wetting: no details	Double blind, randomised controlled trial Entry criteria: age 4 - 10; resistent to previous therapy; no secondary symptoms; no side effects; sufficient information from GPs Follow-up after 4 weeks.	A: 28 improved and 7 showed no change or worsened B: 7 improved and 20 showed no change or worsened. A: 0\35 B: 1\27 Side effects only observed in children under 7 years. Found in both groups	1) German paper 2) No results for severity 3) No details daytime wetting 4) No details of comparability at baseline 5) Not intention to treat 4) No means or sds

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(98) Maxwell, 1971 UK	A: imipramine (25 mg age 5 to 7; 50mg 8 to 12s) + star chart B: placebo + star chart Duration of treatment: 4 weeks each group	135 participants initially. Details of 125 84 boys Age range 5 to 12 yrs Previous treatment: no details Baseline wetting: mean number of dry nights per 28 = 7.0 (7.0)	Multi-centre double-blind, randomised crossover Groups comparable at baseline Entry criteria: Age 5 to 12; normal except for enuresis; wetting 3+ times a week; no organic disease; no MAO inhibitors within previous 2 weeks; home environment guarenteed stable for 8 weeks No follow-up	Mean (sd) number of dry nights per month: A: 16.6 (8.7) B: 13.2 (8.5) Regardless of treatment, results in second month better than first not carry over from drugs - prob due to star charts Side effects A: anorexia (2) diarrhoea (1), constipation (1) and depression. (1) 77 patients prefered imipramine and 22 preferred placebo	1) No details of daytime wetting 2) No washout 3) Not intention to treat 4) Cannot see order effect - crossover results combined 5) Cannot see role of star chart 6)Very short baseline 7) No follow-up
(93) Kolvin, 1972 UK	A: imipramine B: pad and buzzer alarm C: placebo Duration of treatment: 2 months	Number of subjects: A: 35 B: 32 C: 27 2 dropouts 56 boys Mean age: 9.4 yrs (range 8 to 10) Baseline wetting: mean number of wet nights per month A: 22.7 B: 22.0 C: 20.9	Randomised controlled trials Entry criteria: wetting at least 3 nights a week age range (not stated); not receiving treatment elsewhere Follow-up after 4 months	Mean number of wet night in final month (% improvement) A: 9.3 (64) B: 9.1 (62) C: 11.0 (53) At follow-up mean number of wet nights per month (% improvement) A: 13.4 (43) B: 9.3 (64) C: 11.3 (54)	1) No details daytime wetting 2) No details of blinding 3) Not reported if comparable groups 4) Not intention to treat 5) No details previous treatment

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(89) Attenburrow, 1984 UK	A: viloxazine (100mg for under 10s; 150 mg for over 10s) B: imipramine (50mg for under 10s; 75 mg for over 10s) C: placebo Duration of treatment: 7 weeks	Initially 46 participants. After dropouts: A: 12 B: 9 C: 12 11 boys Median age 7 yrs (range 5 to 13) Daytime wetting included Most had received simple preliminary treatments eg lifting and fluid restriction Baseline wetting: mean number of DRY nights in week: A: 2.8 B: 2.4 C: 1.3	Double blind, randomised controlled trial Groups well matched for age and social class and no sig diff in baseline wetting Entry criteria: suitable for drug therapy; parental consent; no abnormalities in blood or urine Follow-up after 2 weeks	Mean number of dry nights in final week: A: 4.4 B: 3.8 C: 1.3 Follow-up: mean number of dry nights: A: 4.1 B: 2.8 C: 1.8 Side effects: A: dizziness and flu with sinus blockage (1); headache (1); lethargy (1). B: lethargy (4); constipation (3); upset stomach (2); vomitting, sweating and shakiness (1); vomitting and drowsiness leading to withdrawal (1); dizziness and dry mouth (1); anorexia (1). C: rash (2); nightmares (1)	1) Includes diurnal and encopresis 2) Few details about dropouts - look to have been more from imipramine group 3) Not intention to treat analysis 3) Follow-up for two weeks only
(91) Fournier, 1987 USA	A: imipramine B: enuresis alarm C: placebo D: random awakening E: alarm + imipramine Duration: 6 weeks	Number of subjects: 64 completed the study 47 boys Mean age: 8 yrs Baseline wetting: mean number of wet nights in week 2 : A: 5.3 B: 6 C: 4.5 D: 4.2 E: 4.5	Double-blind, randomised, controlled trial Differences in baseline severity of wetting - MANOVA used. Entry criteria: no treatment in past 3 months Follow-up after 3 months	Mean number of wet nights per week: A: 1.9 B: 2.5 C: 5 D: 3.3 E: 1	1) No details of diurnal wetting 2) No details of dropouts

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(94) Kumazawa -Ichikawa, 1990 Mexico	A: motivational reinforcement and bladder exercises then placebo B: motivational reinforcement and bladder exercises then 25 mg imipramine Duration of treatment: 6 months	Children with learning difficulties Number of subjects: A: 10 B: 10 No dropouts Boys A: 7 B: 9 Age: mean 8 yrs Previous treatment: various punishments and cold water baths Baseline wetting: mean (sd) wet nights per month: A: 13.2 (9.7) B: 16.6 (7.8)	Blind, randomised controlled trial Groups comparable on all baseline values Entry criteria: aged 6 to 16; 1 wet night per month; no previous treatment; no orgamic causes; no urinary infection; parental consent. No follow-up	Mean number of wet nights A: 3.7 (7.15) B: 8.1 (8.3) By end of study, number achieving 80% reduction in wet nights A: 7 B: 5	1) No details of daytime wetting Unusual participants 2) Small sample groups 3) Severity of enuresis = one wet night during last 3 months! 4) No follow-up 5) Foreign language
(100) Motavalli, 1994 Turkey	A: imipramine - dose depends on age B: clomipramine C: alarm Duration of treatment: 8 weeks	Number of subjects A: 10 B: 9 C: 10 Number of boys A: 6 B: 4 C: 4 Mean age A: 9.1 yrs B: 9.2 yrs C: 8.3 yrs Baseline wetting: mean (sd) number of wet nights in 15 days: A: 9.1 (4.1) B: 11.2 (3.8) C: 10.9 (3.3)	Randomised controlled trial No sig diff between groups in terms of age or IQ Entry criteria: age 5 - 14; no organic causes; normal intelligence; wetting 2+ times a week; no treatment in previous 2 months No follow-up	Mean (sd) frequency of wetting during final two weeks of treatment A: 4.1 (2.6) B: 6.6 (5.5) C: 2.8 (4.3)	1) Foreign langauage 2) No details of daytime wetting 3) Not blinded 4) Unclear if intention to treat 5) No follow-up

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(105) Smellie, 1996 UK	A: imipramine 25 mg B: mianserin: 10mg C: placebo Duration of treatment: 8 weeks	Number of subjects: A: 25 B: 26 C: 29. No dropouts during treatment. Four lost to follow-up Boys A: 19 B: 22 C: 24 Age: 5 to 13 yrs Baseline wetting: mean number of dry nights A: 1.6 B: 1. 6 C: 1	Double blind randomised controlled trial. Randomisation carried out centrally ccording to standar drug trial procedures. Follow-up after 4 weeks	Mean number of dry nights at week 6 (no sds) - from graph A: 5 B; 2.5 C: 2.5 Mean "Wetness score": A: 3 B: 5.6 C: 6 Number of children achieving SEVEN consecutive dry nights A: 21 B: 9 C: 7 After 4 weeks without treatment, % showing some improvement A: 74 B: 54 C; 59	1) Graphical data 2) No standard deviations 3) Diurnal wetting not excluded 4) No reported comparable groups 5) No details previous treatment 6) Follow-up not intention to treat
(112) Harrington, 1960 UK	A: phenmetrazine (preludin) 25 mg: half tablet for young children; 2 tablets for adults B: placebo no fluid restrictions, diet change and no lifting Duration of treatment: 1 month each group	Number of subjects: 11 1 dropout 8 boys Age range 5 to 16 yrs (and one aged 31 yrs) 1 had daytime wetting Previous treatment: 1 resection of bladder neck Baseline wetting: mean number of wet nights per month A: 26.7 B: 22	Randomised double crossover trial Exclusion criteria: ascertainable organic disease No follow-up	Mean (sd) number of wet nights period 1: A: 7.3 (7.06) B:11 (6.83) period 2: A: 3.3 (1.50) B: 5.2 (6.62) period 3: A: 1.3 (1.75) B: 3.8 (2.5)	1) Very small sample 2) Groups do not look comparable 3) Dropout not included in analysis 4) Includes one adult - should not 7group all patients together 5) No follow-up 6) Clear carry over effect period 1 to 2

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(109) Gjessing, 1968 Denmark	A: chlorprotixine (Truxal) 5mg B: placebo Crossover Duration of treatment: 6 weeks each group	Number of subjects 69 24 dropouts 37 boys Age; 70% age between 4 and 7 yrs Baseline wetting: wet bed at least 4 x week for those under 7 and 2+ week for those over 7	Randomised cross over trial Entry criteria: age 4+; 4+ wet nights for < 7yrs; 2+ wet nights for 7+; no organic causes; no previous treatment	Number of children achieving 100% dry nights A: 4 B: 2	1) Danish translation 2) Results not clear 3) Design questionable. 4) No details of daytime wetting
(110) Liederman, 1969 USA	A: desipramine (dosage depends on age - usually 50 to 75mg) for 60 days B: placebo Duration of treatment: 60 days	Initial number of subjects: 109. Results from A: 53 B: 47 71 boys Age range 6 to 22 yrs (mainly less than 12 yrs) Severity of wetting: range from 5 to 80 bedwetting incidents per month with at least 20 per month for most patients	Double-blind randomised controlled trial. Entry criteria: diagnosis of functional enuresis No follow-up	number (%) achieving 50% decrease in wetting after 1 month: A: 27 (51) B: 13 (28) number (%) with considerable improvement" after 2 months: A: 32 (60) B: 21 (45) Number completely dry after 2 months: A: 12 B: 3 4 children and 1 adult had side effects: postural hypotension, mild abdominal cramps and headaches	1) No details of daytime wetting 2) Comparability of groups not reported 3) Not intention to treat analysis 4) No follow-up

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(108) Wright, 1974 USA	A: (2.5mg) amphetamine sulphate B: 75mg ephedrine sulphate + 1.15mg atropine sulphate (Enuretrol) C: placebo twice daily D: enuresis alarm Duration of treatment: 5 weeks	Number of subjects: A: 3 B: 5 C: 5 D: 10 Age range 4 to 10 yrs Baseline wetting: Mean number of wettings per week: A + B: 4.9 C: 3.0 D: 6.6 Dropouts: A: 0 B: 0 C: 2 D: 0	Randomised controlled trial - medications on double blind basis Follow-up after 4 weeks	Mean number of wet nights in final week of treatment A+ B: 4.1 C: 3.5 D: 1.7	1) No details of daytime wetting 2) Groups seem very different at baseline 3) More likely to detect more wettings per night in pad and bell group 4) All active drugs groups combined 5) No details of dropouts 6) No details of inclusion\exclusion criteria
(111) Lovering, 1988 Canada	A: 2 x 5mg tablets oxybutynin at supper time B: identical placebo Duration of treatment: 28 days in each group	41 participants; 11 dropouts 25 boys and 5 girls Mean age: boys 9.7 yrs; girls 10.4 yrs Previous treatment: 4 (13%) never had drug therapy 22 treated with imipramine; 6 with unknown drugs Baseline wetting: mean number of wet nights: 20 out of 28	Double-blind, randomised crossover Entry citeria: history compatable with primary nocturnal enuresis; no history of urinary tract surgery; no urinary tract infection; no daytime wetting	Mean diff in frequency of wet nights while taking oxybutynin rather than placebo was -1.87 No sig diff between boys and girls (pooled sample variance = 56.9, t = 0.61, p = 0.55) or between those who had previously taken imipramine and those who hadn't Mild side effects (stomach discomfort, fatigue, dizziness, headache and dry mouth) noted in 5/30	1) Not reported if comparable groups 2) No washout 3) Not intention to treat 4) No follow-up 5) 25% dropped out!! 6) Graphical data

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(118) Scholander, 1968 Sweden	First week A + B enuresis alarm but switched off 2nd week A: enuresis alarm + noritriptyline B: enuresis alarm + placebo Duration of treatment: 5 weeks	Number of subjects A: 15 B: 15 No dropouts 23 boys Age range 7 to 17 yrs Previous treatment: all had received imipramine, amitriptyline or nortriptyline Baseline wetting: wet bed between 2 and twelve times a week	Double-blind randomised controlled trial Groups comparable in age and frequency of wet nights Follow-up after 6 to 12 months	Number with no wet nights in final week of treatment A: 9/30 B: 6/30	1) Swedish paper 2) No details of daytime wetting 3) No details of inclusion\exclusion criteria
(119) Sloop, 1973 USA	A: enuresis alarm B: control - usual "potting" procedure - taken to the toilet twice a night Duration of treatment: 11 weeks	Learning disabled children in residential training centres Number of subjects: A: 21 B: 21 Number of boys: A: 11 B: 11 Mean age : A: 13 yrs B: 12 yrs (range 7 to 18) Previous treatment: none Baseline wetting: mean number of wet nights: Boys: A: 4.18 B: 4 Girls: A: 3.64 B: 3.54	Initially RCT - Subjects paired on IQ, sex, age and number of wet nights during baseline then one from each pair randomly allocated to conditions Males and females analysed separately Exclusion criteria: epileptics; severe behaviour problems; encopretics; residents in beds with side rails which prevent them arising; residents on nightly tranquilising medications; measured IQ below 20; not wetting bed at least once during baseline	Number of wet nights after 7 weeks (boys) A: 46 B: 108 $p < 0.01$ No sig diff for girls (no data) Number (%) totally dry: Boys A: 7 (64) B: ? Girls A: 4 (40) B: ?. One child in Gp B totally dry $p< 0.01$ 4 of 11 relapsed	1) No details of daytime wetting 2) Not clear if intention to treat 3) One pair of boys switched after 3 nights of treatment

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(107) Danquah, 1975 Ghana	A: traditional shaming B: Amitriptyline Hydrochloride C: enuresis alarm Duration of treatment: 7 weeks	Ghanian fishing community Number of subjects: A: 10 B: 10 C: 10 All boys Mean age: 10.4 yrs Mean frequency of wetting at baseline: A: 5.6 B: 4.00 C: 3.20	Randomised controlled trials - mention of matching Groups comparable in age and intelligence Exclusion criteria: more than a week of traditional treatment Follow-up after 3 months	Mean frequency of wetting after treatment: 5.6 B: 4.00 C: 3.2. Subjects of traditional shaming seemed depressed and evidence of loss of self esteem and patients isolating themselves from friends. Drug treatment was said to cause drowsiness at first. Parents not disturbed by alarm because they slept outside	1) No details of daytime wetting 2) No details of dropouts 3) No details of previous treatment
(120) Taylor, 1975 UK	A: continuous B: intermittant - 59% reinfocement schedule C:overlearning When achieved initial success fluid intake increased by 1-2 pints prior to going to bed Duration of treatment: until no more than 1 wetting incidence in 28 days	Number of subjects: 82 68 boys Age range 4 to 15 yrs: mean boys = 8.8 yrs mean girls = 9.3 yrs Daytime wetting: 16 participants Baseline wetting: no details Number of dropouts unclear because some subjects replaced by next admission to enuresis clinic	Randomised controlled trial (sequential allocation). Results from 61 participants analysed Entry criteria: Aged between 4 and 16 parents saw enuresis as a problem; no relevant organic pathology Follow-up after 3 months	Number (%) achieving no more than one wetting incidence in 28 days: A: 13 (62) B: 9 (50) C: 13 (59) Number (%) of successes who relapsed A: 9 (69) B: 4 (44) C: 3 (23)	1) Comparability of groups not reported 2) Not intention to treat 3) No details of previous treatment 4) Includes both diurnal wetting and encopresis

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(117) Jehu, 1977 UK	A: no treatment control B: enuresis alarm Duration of treatment: 3 or 4 months - until success achieved	Children resident in Children's Homes Number of subjects A: 20 B: 19 Boys A: 17 B: 8 Mean age 9.4 yrs (range 4.9 yrs to 14.7 yrs) Previous treatment: 7 children had had drug therapy and in two cases alarm treatment had been used. Baseline wetting: For treatment group only mean no wet nights per week = 4 1 dropout	Randomised controlled trial More girls in alarm group Analysis curtailed after 12 weeks to accomodate the loss of some control children. Entry criteria: Age 4 years or over; wetting frequency of at least 4 nights per week during baseline; attending normal rather than special school; not previously treated by alarm within last year; no gross physical handicap; treatment not impractical -eg children only spent weekends or school holidays at the home Followed up after 6 months then 20 months	Mean number of wet nights in week 12: A: 0. B: 5.3 A: alarm 18 out of 19 reached success criterion. One had absconded so counted as failure Within first 6 months 3 children had relapsed so as to need repeat treatment and another at 32 weeks	1)No details of daytime wetting 2) Comparability of groups not reported 3) No baseline for control - prob should compare from week 4) For control to compensate for this 4) Not intention to treat

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(114)A Bollard, 1981 Australia	A: enuresis alarm - supervised (weekly follow-up) B: enuresis alarm - unsupervised C: waiting list control Duration of treatment: until achievement of 14 consecutive dry nights or 20 weeks	Number of subjects: A: 15 B: 15 C: 15 Number of boys:A: 11 B: 11 C: 10 Mean age: A: 9.10 yrs B: 9.9 yrs C: 9.5 yrs Baseline wetting: Mean number of wet nights per week: A: 5.3 B: 5.4 C: 4.2 Number of dropouts: A: 0 B: 3 C: 0	Randomised controlled trial Two analyses: a) intention to treat basis; b) excluding dropouts Exclusion criteria: No underlying organic pathology Follow-up after 3, 6 and 12 months	Mean number of wet nights at end of 20 weeks: intention to treat;: A: 0.8 B: 2.2 C: 4.6 Intention to treat analysis 2 treatment groups did not differ significantly in number of wet beds at end of 20 weeks or number of days taken to reach dryness criterion. Number achieving 14 consecutive dry nights A: 12 B: 9 C: 0 Number relapsing at 12 mth follow-up A: 4 B: 5	1) No details daytime wetting 2) No blinding 3) Comparability of groups not reported 4) Graphical data 5) No baseline data for control group 6) No details of previous treatment
(121) Wagner, 1985 USA	A: contiguous enuresis alarm: B: delayed response enuresis alarm - 3 second delay C: waiting list control Duration of treatment: 12 weeks	Number of subjects: A: 13 B: 13 C: 13 20 boys mean age: 7.9 yrs (range: 5 to 14) severity at baseline: % wet nights per week: A: 80 B: 83 C: 90 No dropouts	Randomised controlled trial Clinicians blind to specific purpose of the study No sig diff in gps Entry criteria: between 5 and 16 years old; IQs not less than 70; no physical or neurologic disorders as assessed by the child's physician; wet the bed at least 3 nights a week before treatment; not had conditioning treatment for at least a year; agreed to random assignment Follow-up after 6 months	Percentage of wet nights per week in week 12 A: 5.38 B: 20.67 C: 72.90 Number achieving 14 consecutive dry nights: A: 8 B: 7 C: 1 Number relapsing A: 2 B: 5 Malfunction sig greater problem for delayed alarm as compared with contiguous model	1) Poor randomisation 2) No details of daytime wetting 3) No details of previous treatment

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(116) Geffken, 1986 USA	A: alarm - large MFBC B: alarm - small MFBC C: alarm + RCT - large MFBC D: alarm + RCT - small MFBC (MFBC = mean functional bladder capacity) Duration of treatment: 14 weeks	Number of subjects: initially 50 A: 10 B: 10 C: 10 D: 10 Boys: A: 8 B: 5 C: 6 D: 6 Mean age A: 9.0 yrs B: 7.7 yrs D: 9.4 yrs E: 8.0 yrs Baseline wetting: Mean (sd) number of wet nights per week A: 4.9 (1.7) B: 5.7 (1.3) C: 5.4 (1.1) D: 4.9 (1.2) 10 dropouts	Half children with small MFBC and half with large randomly allocated to conditions For those who completed treatment no signif diff between the groups in terms of sex , age, child adjustment measures or the Tolerance and Nuisance Scales. Entry criteria: nocturnal enuresis of at least 3 months duration with 2+ nighttime wetting episodes a week Follow-up after 8 or more weeks	Mean (sd) number of wet nights per week A: 1.7 (1.2) B: 2.3 (1.0) C: 2.5 (0.9) D: 1.6 (1.1) Sig interaction between MFBC and treatment F(1, 33) = 4.90, p 0.03 Number of children achieving initial arrest during 14 weeks treatment A: 9 B: 10 C: 9 D: 9 Number of children relapsing during follow-up A: 3 B: 6 C: 4 D: 3 NS	1) No details of daytime wetting 2) Not intention to treat analysis 3) Short follow-up 4) No details of previous treatment 5) Payment required

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(53) Butler, 1988 UK	A: standard enuresis alarm treatment B: modified Dry Bed Training - enuresis alarm in conjunction with DBT method with positive practice trials and reprimands during cleanliness training eliminated. Duration of treatment: 16 weeks	Number of subjects: Originally 74 but 11 excluded after baseline A: 28 B: 35 Boys: A: 18 B: 29 Mean age: A: 8.99 yrs B: 9.86 yrs Previous treatment: 36 (48.6%) previously treated with enuresis alarm Baseline wetting: mean number of dry nights during 4 weeks A: 1.07 B: 1.02 Dropouts: A: 8 B: 6	Randomised controlled trial No sig diff between groups for demographic factors BUT DBT-M group more likely to have previously used alarm. Analysis of covariance adjusted for the effects of previous experience with enuresis alarm. Entry criteria: age at least 6 years;wetting at least five nights a week for a month; normal clinical exam; normal urine on microscopy; normal intelligence (assessed by reference to educational background and parental-child interview); not having any form of enuresis related drug or psychotherapeutic treatment No follow-up	Mean number of dry nights in last 4 weeks A: 20.76 B: 23.79 $F(1,46) = 1.77$ Percentage of children achieving 14 dry night criterion A: 70 B: 70 no sig diff Mothers in dropout group sig more angry with bedwetting than other groups	1) No details daytime wetting 2) No blinding 3) Not intention to treat 4) No follow-up

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(56) Sukhai, 1989 Netherlands	A: enuresis alarm and bedtime dose of 20 mcg DDAVP B: enuresis alarm and bedtime dose of placebo Duration of treatment: 2 weeks in each group	28 participants 21 boys Mean age: 11 yrs (range: 7 to 16 yrs) Previous treatment: 19 had previous attempts at treatment including alarm (n = 9) and tricyclic antidepressants (n = 10) Severity at baseline: mean (sem) number of DRY nights per week = 1.4 (0.3) No dropouts.	Double blind randomised cross-over with 2 weeks washout Entry criteria: Normal urine concentration capacity of 800 mosmol/kg or higher; 3 or more wet nights per week during observation period; informed parental consent; no urological or renal disorder; no history of daytime wetting; no chronic urinary tract infection; no neurological cardiovascular disease Follow-up: 4 weeks to 6 months	Mean (sem) dry nights during treatment: A: 5.1 (0.4) B: 4.1 (0.4) 6wk follow-up:14 dry, 5 relapsed 4.5 month follow-up: 9 remained dry No adverse side effects Mean urine osmolality signif increased from baseline Signif higher urine osmolality with DDAVP than placebo No adverse effects. Steady significant increase in body weight	Very good study
(113)A Butler, 1990 UK	A: pad and bell alarm B: body worn alarm Duration of treatment: 16 weeks	Number of subjects: A: 20 B: 20 Boys A: 14 B: 11 Mean age: A: 8.2 yrs B: 9.1 yrs Previous treatment: None Baseline wetting: mean number of DRY nights per week: A: 1.2 B: 0.7 Dropouts A: 3 B: 2	Randomised controlled trial No sig diff between groups on any variable Entry criteria: wetting at least 4 nights a week for a month; nomal physical examination; normal urine microscopy; normal intelligence (assessed by reference to educational background and parent\child interview); not previously treated for nocturnal enuresis Follow-up after 6 months	Mean number of wet nights in 16 weeks: A: 18.9 B: 15.3 Number (%) children achieving 14 consecutive dry nights: A: 14 (70) B: 14 (70) Mean number of wet nights until achievement of 14 consecutive dry nights A: 54.8 B: 35.3 Number (%) children relapsing:A: 4 (29) B: 3 (21)	1) No details of daytime wetting 2) No blinding 3) Unclear if intention to treat 4) Poor randomiseation

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(113)B Butler, 1990 UK	A: Modified dry-bed training B: body-worn alarm Duration of treatment: 16 weeks	Number of subjects: A: 24 B: 24 Boys A: 20 B:20 Mean Age: A: 10.2 yrs B: 11.2 yrs Severity at baseline: mean number of DRY nights per week: A: 1.2 B: 1.3 Number of dropouts: A: 2 B 1	Randomised controlled trial Groups did not differ significantly on any variable Entry criteria: wetting at least 4 nights a week for a month; nomal physical examination; normal urine microscopy; normal intelligence (assessed by reference to educational background and parent\child interview); previous unsuccessful treatment with pad and bell alarm; no associated diurnal enuresis Follow-up after 6 months	Mean number of wet nights in 16 weeks A: 28.7 B: 25.0 Number (%) attaining 14 consecutive dry nights A: 14 (58) B: 20 (83) Mean number of wet nights to achievement of 14 consecutive dry nights A: 53.7 B: 40.7 Number (%) children relapsing: A: 7 (50) B: 9 (45) The majority of children preferred body-worn alarm to pad and bell	1) Unclear if intention to treat analysis 2) Poor randomisation
(52) Azrin, 1973 USA	A: enuresis alarm B: Dry Bed Training Duration of treatment: 3 weeks	Residents in a state hospital ward for adults with severe learning difficulties Number of subjects: 12 no dropouts Men: 7 Mean age: 37 yrs Baseline wetting: wet about 50% of time	Randomised controlled trial for 3 weeks then all participants had DBT Entry criteria: wet bed 4\12 nights, no daytime wetting; ambulatory; vision, no medical pathology related to bladder control	Alarm did not significantly reduce wetting. DBT required a mean of 1.4 nights to produce continence	1) No details of comparability of groups 2) Very small groups 3) Alarm only tried for 3 weeks 4) No details previous treatment

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(114)B Bollard, 1981 Australia	A: Dry Bed Training (DBT) with therapist at home B:DBT with therapist at hospital C:DBT with parents as therapists at home D:DBT - parents as therapists at home - WITHOUT enuresis alarm. E:alarm F: waiting list control Duration of treatment: until 14 consecutive dry nights or 20 weeks	Number of subjects: A: 20 B: 20 C: 20 D: 20 E: 20 F: 20 12 dropouts in D Number of boys: A: 14 B: 13 C: 16 D: 14 E: 14 F: 11 Mean age: A: 9.3 yrs B: 8.11 yrs C: 9.7 yrs D: 8.6 yrs E: 8.8 yrs F: 8.10 yrs Baseline wetting: mean number of wet nights: A: 5.8 B: 5.2 C: 6.0 D: 5.7 E: 6.0 F: 4.7	Randomised controlled trial Analysed on intention to treat basis and with dropouts excluded Entry criteria: thorough medical examination; regularly wetting at least one night per week; no other treatment during trial Follow-up after 3, 6 and 12 months	Comparing DBT with alarm only - DBT sig more effective in terms of number of wet nights and days to dryness Mean number of wet nights per week at end of week 20 (inc dropouts) A: 0 B: 0 C: 0 D: 3.8 E: 4.4 (exc dropouts) A: 0 B: 0 C: 0 D: 1.3 E: 4.4 Number achieving 14 consecutive dry nights: A: 20 B: 20 C: 20 D: 5 E: 16 F: 2 $p < 0.05$ Number relapsing: A: 5 B: 6 C: 4 D: 2 E: 6 F: 2 NS	1) No details of daytime wetting 2) No details of blinding 3) DBT no alarm group younger than others and more girls in waiting list control 4) No details previous treatment

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(123) Bollard, 1982 Australia	A: alarm only B: alarm (A) + waking schedule (W) C: A+retention control training (RCT) D: A+ positive practice (PP)+ cleanliness training (CT) E: A+W+RCT F: A+W+PP +CT G:A+RCT+PP +CT (H: Full DBT) Duration of treatment: 20 weeks	Number of subjects:127 (2 groups combined) 88 boys Mean age 9.10 yrs Previous treatment: many had previously sought help but none undergoing any form of enuresis related drug or psychotherapy at the time of the study. Baseline wetting: Overall mean number of wet nights per week = 5.5	Mainly RCT but also comparison with previous study: A and H from another study Entry criteria: no underlying organic pathology No follow-up	Mean number of wet nights during 20 week treatment period A: 27 B: 13 C: 24 D: 23 E: 14 F: 10 G: 21 H: 11 Number of cases becoming dry: A: 31 B: 12 C: 11 D: 10 E: 12 F: 12 G: 11 H: 20 Sig diff in response rate of gps with waking schedule and those without - Chi squared = 13.04, df = 3, $p < 0.01$	1) Groups A and H from another trial 2) No details daytime wetting 3) No analysis of comparability of groups 4) No blinding 5) No follow-up
(124) Bollard, 1982 Australia	A: DBT + alarm B: DBT without alarm C: no treatment control Duration of treatment: 8 weeks	Number of subjects: A: 10 B: 10 C: 10 no dropouts 18 boys Mean ages: A: 8.5 yrs B: 9.4 yrs C: 9.5 yrs Baseline wetting: mean number of wet nights per week: A: 4.9 B: 5.0 C: 5.3	Randomised controlled trial Groups comparable at baseline Entry criteria: no underlying organic pathology Follow-up after 3 months	Mean number of wet night per week (final week): A: 0.2 B: 3.25 C: 5.3 Number of children achieving 14 consecutive dry nights: A: 9 B: 2 C: ? 30 children underwent DBT with alarm and 29 achieved success criterion within 16 weeks Number relapsing: A: 3 B: 4	1) No details daytime wetting 2) No blinding 3) Not intention to treat 4) No details of previous treatment

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(122) Bollard, 1982 Australia	A: DBT + alarm B: alarm only relapses wanting retreatment to resume daily monitoring for 4 weeks. DBT group not given not intensive first night Duration of treatment: Initially until 14 consecutive dry nights or 20 weeks	Number of subjects 89 out of 95 A: 60 B: 35 68 boys Mean age 9.3 yrs (range 5 to 15) Baseline wetting: mean number of wet nights: A: 5.8 B: 5.2 C: 6.0 D: 5.7 E: 6.0 F: 4.7	Randomised controlled trial Follow-up at 3, 6, 12 and 24 months after child reached dryness criterion Entry criteria: see (114)B. Those wanting retreatment after relapse	Number (%) of children who relapsed 3 mth A: 6 (10) B: 6(19) 6 mth A: 13 (22) B:7(23) 12 mth A:15 (26) B:10(35) 24 mth A:22 (39)B: 12(41) Retreatment: Renewed bedwetting frequency was sig lower than baseline frequency $F(1,23) = 30.48$ $p < 0.01$). No overall treatment effect Only those with a history of diurnal wetting incidents were found to be more likely to suffer relapse. Age, sex, primary\secondary nature unrelated to relapse	1) No details daytime wetting 2) No blinding 3) Not reported if comparable groups 4) Unclear if intention to treat 5) No details previous treatment 6) Follow-up study of (114)B

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(125) Keating, 1983 USA	A: DBT with office training for parent and child B: DBT with in home training for parent and child C: DBT with office training for parent only D: waiting list control Duration of treatment: 5 weeks	Number of subjects: A: 7 B: 9 C: 7 D: 7. No dropouts until follow-up 18 boys mean age: 8.1 yrs (range: 4 to 14) severity: wet at least 50% of nights	Randomised controlled trial. No sig diff between groups in terms of age. Entry criteria: diurnally continent; child must be able to follow simple instructions; organic factors ruled out by a physician Follow-up after 5 months	Mean number of DRY nights per week in final treatment week A: 4.3 B: 4.5 C: 5.1 D: 5.0 Number of children achieving 14 consective dry nights: A: 7 B: 5 C: 6 NS Number of children relapsing: A: 2 B: 2 C: 2 No differences among treatment groups in terms of parental self-reports of consistent supervision and conduct of training following initial instruction, nor differences in terms of parental satisfaction with DBT programme	1) No blinding 2) No details of previous treatment 3) No information about control group after 5 weeks 4) Only graphical data

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(126) Harris, 1977 Canada	A: bladder training in a camp\treatment program followed by parental training B; waiting list control Duration of treatment: Stage 1: 5 days; stage 2: 30 days	Number of subjects: A: 9 B: 9 Boys A: 5 B: 7 Mean age A: 9.2 yrs B: 8.8 yrs (range 5 to 13) Daytime wetting: none Half subjects had previously taken medication but discontinued because it was ineffective or because of side effects. Baseline wetting: mean number of wet nights per week: A: 3.2 B: 5	Randomised controlled trial Entry criteria: 1+ wet night per week Follow-up after 9 weeks	Mean number of wet nights per week A: 2.6 B: 5.0 No sig group, time or interaction effects At follow-up mean wetting of expt gp = 3.9 nights which not sig diff from pre or post-treatment measures ($F = 1.68$, $df = 2, 16$) Sig main effect of time on bladder capacity ($F = 5.73$, $df = 1,16$, $p < 0.05$) and sig group\time interaction ($F = 5.02$, $df = 1,16$ $p < 0.05$) graphs suggest this due to increased bladder capacity in expt group	1) No blinding 2) Comparability of groups not reported 3) Unclear if intention to treat 4) Short follow-up 5) Inapproriate control
(115) Fielding, 1980 UK	A: retention Control Training and enuresis alarm B: enuresis alarm Duration of treatment: (4 weeks RCT) and 14weeks for alarm	Number of subjects: 45 (6 lost at baseline) 30 boys Age range 5.2 yrs to 13.10 yrs Baseline wetting: mean number of wet nights in 4 week baseline: A: 23.5 B: 24.7 11 dropouts	Randomised controlled trial Analysed on intention to treat basis Entry criteria: Age 5 to 15; no urinary tract infection; no evidence of organic pathology; not treated within previous 12 months; no daytime wetting Follow-up after 3, 6 and 12 months	Mean number of wet nights in 3rd month of alarm A: 6.2 B: 2.3 Number achieving 14 consecutive dry nights A: 11 B: 14 Number (%) remaining dry after 3 mth A: 8 (73) B: 10 (71) 6 mth A: 8 (73) B: 9 (64) 12m A: 7 (66) B: 6 (43)	1) Parallel study specifically includes diurnal wetters 2) No blinding 3) Not reported if comparable groups

Study Ref, Author, Country	Intervention	Participants	Design	Results	Comments
(127) Leboeuf, 1991 Australia	A: 2 week waiting list control before chiropractic treatment B: specific chiropractic adjustments of the area(s) of aberrant spinal movement as detected on each visit through observation and palpitation Duration of treatment: Until fewer than two wet nights within 14 days - up to 8 visits if no response.	Number of subjects: A: 71 B: 100 Boys A: 76% B: 66% Mean age: A: 8.5 yrs B: 8.3 yrs Previous treatment: 70% had previous treatment for bedwetting Baseline wetting: Median number of wet nights per week A: 4.8 B: 6.0 A total of 163-167 evaluated through out various stages of study	RCT - but only for two weeks. Not analysed as such Sig diff in initial estimate of severity of wetting Exclusion criteria: daytime wetting or soiling at any time; anatomical \physiological abnormalities; recurrent urinary tract infections; infrequent wetting (less than one wet night per week; possible or definate contraindications to spinal manipulative therapy; absence of indication for spinal manipulative therapy as determined by the examining chiropractor	Median number of wet nights per week A: control: 5.0 B: chiropractic:5.6 (from graph)	1) No blinding 2) Groups not comparable 3) Not intention to treat 4) No follow-up 5) No comparison with control 6) Results from graph
(128) Edwards, 1985 South Africa	A: trance plus suggestions B: suggestions without trance C: trance alone D: waiting list control Duration of treatment: six standardised weekly sessions lasting an hour each	Number of subjects: A: 12 B: 12 C: 12 D: 12 no dropouts reported Boys only Mean age 10.5 yrs (range 8 to 13) Baseline wetting: mean number of dry nights per week: A: 2.7 B: 2.0 C: 3.8 D: 2	Randomised controlled trial Exclusion criteria: organic pathology; diurnal wetting Follow-up after 6 months	Mean number of dry nights per week: A: 4.3 B: 4.6 C: 5.1 D: 2.18	1) Comparability of groups not reported 2) Unclear if intention to treat 3) No details previous treatment

Appendix 5
Reasons for Exclusion of Studies from Review

Author	RCT	Comparison group	Systematic baseline	Systematic outcomes	Organic causes excluded
(210) Abrams, 1963	no	yes	no	yes	yes?
(211) Adler, 1959	no	yes	no?	Yes	no?
(212) Al Waili, 1986	no	yes	no	yes	yes
(213) Alderton, 1967	no	yes	yes?	yes	no
(214) Alderton, 1970	no	yes	yes?	yes	no
(215) Alison, 1973	no	yes	no	no	no
(216) Arai, 1971	no	yes	no	yes	yes
(217) Arajarvi, 1977	no	yes?	No	yes?	yes
(218) Arroe, 1979	no	no	no	yes	yes
(193) Azrin, 1974	yes	yes	no	yes	no
(194) Azrin, 1978	yes	yes	no	yes	no
(219) Azrin, 1979	no	no	yes	yes	yes?
(220) Baller, 1956	no	no	no	yes	no
(221) Baller, 1970	no	no	no	yes	no
(59) Bartocci, 1981	no	yes	no	yes	no
(222) Bergman, 1976	no	no	no	yes	no
(223) Berhle, 1956	no	no	no	yes	yes
(224) Bernasconi, 1992	no	yes	yes	yes	no
(225) Besalel, 1980	no	no	no	yes	no
(226) Bhatia, 1990	no	yes	no	no	yes
(227) Boggs, 1992	no	no	yes	yes	yes
(228) Bollard, 1977	no	yes	no	yes	yes
(229) Bouchard, 1981	no	yes	yes	yes	no
(230) Butler,	no	no	no	yes	yes
(69) Butler, 1990	yes	yes	no	yes	no
(231) Buttarazzi, 1977	no	no	no	yes	yes

Author	RCT	Comparison group	Systematic baseline	Systematic Outcomes	Organic causes excluded
(232) Cai, 1987	no	??	No	yes	no
(233) Ceresoli, 1993	no	no	no	yes	no
(234) Cigna, 1989	no	no	no	no	no
(235) Collins, 1973	no	yes	no	yes	no
(236) Cortina, 1994	no	no	no	yes	no
(237) Creer, 1975	no	no	yes	yes	no
(238) Crisp, 1984	yes	yes	no	no	no
(239) Danielsson, 1985	no	no	no	yes	no
(240) Davidson, 1950	no	no	no	yes	yes
(241) De Castro, 1985	no	no	yes	yes	yes
(242) de Jonge, 1972	no	yes	no	yes	yes
(243) Devlin, 1990	no	no	yes	yes	yes
(244) D'Hollander, 1967	no	yes	no	yes	no
(243) Devlin, 1990	no	no	yes	yes	yes
(245) Dimson, 1986	yes	yes	no	yes	no
(246) Dische, 1971	no	no	no	yes	yes
(247) Doeschate, 1994	no	no	no	yes	yes
(195) Dorison, 1962	yes	yes	no	yes	no
(248) Eckford, 1994	yes	yes	no	no	no
(249) Edelstein, 1984	no	no	yes	yes	no
(250) Egger, 1992	no	yes	no	yes	no
(251) el-Sadir, 1990	no	yes	no	yes	yes
(252) Elmer, 1988		DIURNAL			
(253) Elmer, 1991		DIURNAL			
(251) el-Sadir, 1990	no	yes	no	yes	yes
(254) Elzinga-Plomp, 1995	no	no	no	yes	yes
(196) Fava, 1981	yes	yes	no	yes	no
(255) Figueroa, 1995	no	no	no	yes	yes
(256) Finley, 1973	no	yes	no	yes	yes
(257) Finley, 1976	no	no	no	yes	no
(258) Finley, 1982	no	yes	no	yes	no

Author	**RCT**	**Comparison group**	**Systematic baseline**	**Systematic outcomes**	Organic causes excluded
(259) Fly-Hansen, 1995	no	no	no	yes	no
(197) Forrester, 1964	yes	yes	no	yes	no
(260) Forsythe, 1969	yes	yes	no	yes	no
(261) Forsythe, 1970	no	no	no	yes	yes
(262) Freyman, 1963	no	no	no	yes	no
(263) Fritz, 1994	no	no	yes	yes	yes
(64) Gemmell, 1989	no	no	?	?	?
(264) General Practitioner Research Group, 1969	no	yes	no	yes	yes?
(265) Geppert, 1953	no	no	no	yes	yes
(266) Gillison, 1958	no	no	no	yes	no
(267) Goel, 1984	no	yes	no	no	yes
(268) Grassetti, 1986	no	no	yes	yes	yes
(269) Griffiths, 1982	no	no	yes	yes	yes
(270) Hagglund, 1964	no	yes	no	yes	yes
(271) Halliday, 1987		DIURNAL			
(198) Hicks, 1964	yes	yes	no	yes	no
(272) Hjalmas, 1995	no	no	yes	no	no
(273) Hofler, 1978	no	no	yes	no	yes
(54) Houts, 1983	no	??	no	yes	no
(274) Hunt, 1989	no	no	yes	yes	yes
(275) Ishigooka, 1992	no	no	yes?	yes	yes?
(276) Jarvis, 1982	no	no	no	yes?	yes
(140) Jensen, 1982	no	yes	yes	yes	yes
(277) Jones, 1959	no	yes	no	yes	no
(278) Jorgensen, 1980	no	yes	no	yes	?
(279) Kahane, 1955	no	yes	no	yes	yes
(280) Kales, 1977	no	no	yes	yes	yes?
(281) Kamel, 1969	no	no	no	yes?	yes?
(282) Kaplan, 1989	no	yes	no	yes	yes
(283) Kapoor, 1969	no	yes	no	yes	yes

Author	RCT	Comparison group	Systematic baseline	Systematic outcomes	Organic causes excluded
(284) Kardash, 1968	no	yes	no	yes	yes
(285) Key, 1992	no	no	no	yes	yes
(286) Kondo, 1988	no	no	yes	yes	yes
(199) Kooijman, 1986	yes	yes	no	yes	no
(287) Korczyn, 1979	no	yes	yes	yes	no
(288) Kurokawa, 1963	no	no	yes	yes	yes
(289) Kyneb, 1975	no	no	no	yes	yes
(290) Lake, 1968	yes	yes	no	yes	no
(291) Lake, 1979	yes	yes	no	no	no
(292) Li, 1992	no	no	no	yes	no
(293) Libert, 1991	no	no	yes	yes	yes
(200) Lindholm, 1967	yes	yes	no	yes	no
(294) Lines, 1968	no	yes	no	yes	no?
(295) Lovibond, 1963	no	no	no	yes	yes
(296) Lovibond, 1964	no	yes	no	yes	yes
(297) Luiselli, 1987		DIURNAL			
(298) Manglick, 1992	no	yes	no	yes	no
(299) Marshall, 1973	no	yes	no	yes	yes
(300) Matthiesen, 1994	no	no	yes	yes	yes
(301) Mayon-White, 1956	no	Yes	no	yes	yes
(201) McConaghy, 1969	yes	yes	no	yes	no
(302) Meadow, 1982		DIURNAL			
(303) Meijer, 1965	no	no	yes	yes	yes
(304) Miller, 1968	no	yes	yes	yes	no
(305) Miller, 1988	no	no	no	yes	yes
(306) Miller, 1989	no	no	yes	yes	yes
(61) Minni, 1990	no	yes	no	yes	yes
(307) Mishra, 1980	no	yes	no	no	yes
(308) Monda, 1995	no	yes	no	yes	yes
(309) Motta, 1979	no	no	no	yes	yes
(310) Noack, 1964	no	yes	no	yes	no

Author	RCT	Comparison group	Systematic baseline	Systematic outcomes	Organic causes excluded
(311) Olness, 1975	no	no	no	yes	yes
(312) Paschalis, 1972	no	yes	no	yes	no
(313) Persson-Junemann, 1993	no	no	no	yes	no
(314) Petersen, 1971	no	yes	no	yes	no
(315) Petersen, 1974	no	yes	yes	yes	no
(316) Peterson, 1969	no	yes	yes	yes	no
(317) Philpott, 1970	no	no	no	yes	yes
(318) Polak	no	yes	no	no	no
(319) Porot, 1970	no	yes?	Yes?	yes	no
(101) Poussaint, 1965	no	yes	no	yes	yes
(320) Poussaint, 1965	no	no	yes	yes	yes?
(321) Protinsky, 1983	no	no	no	no	yes
(322) Ramsden, 1982	no	yes	no	yes	yes
(323) Ritvo, 1969	no	yes	yes	no	yes
(324) Rodriguez, 1995	no	no	yes	no	yes
(62) Roje-Starcevic, 1990	no	no	no	yes	no
(205) Rushton, 1995	no	yes	yes	yes	no
(325) Sacks, 1973	no	no	yes	yes	no
(326) Sacks, 1983	no	no	no	yes	no
(327) Sacks, 1973	no	yes	no	yes	no
(202) Salmon, 1973	yes	yes	no	yes	no
(328) Schulz, 1978	no	yes	yes	yes	yes
(329) Shah, 1971	yes	yes	no	no	yes
(330) Simeon, 1981	no	no	yes	yes	no
(331) Singh, 1980	no	yes	no	yes	no
(332) Site, 1974	no	yes	no	yes	yes
(333) Smith, 1967	no	yes	yes	yes	no
(334) Smith, 1981	no	no	yes	yes	no
(335) Soulayrol, 1970	no	yes	yes	yes	no
(336) Steffens, 1993	no	no	no	no	yes
(337) Steinicke, 1971	yes	yes	no	yes	no

Author	RCT	Comparison group	Systematic baseline	Systematic outcomes	Organic causes excluded
(338) Stenberg, 1993	no	no	yes	yes	no
(339) Stenberg, 1995	no	no	yes	yes	no
(340) Taylor, 1963	no	no	no	yes	yes
(341) Tiptaft, 1984	no	no	no	yes	yes
(342) Tosto, 1989	no	yes	no	no	yes
(343) Tret'iakova, 1990	no	no	no	yes	yes
(344) Turner, 1974	no	no	yes	yes	yes
(345) Turner, 1966	no	yes	no	yes	yes
(346) Turner, 1970	no	yes	no	yes	yes
(88) Tuvemo, 1978	no	no	no	yes	yes
(347) Ulf, 1964	no	yes	no	yes	no
(348) van Londen, 1993	no	yes	no	yes	no
(349) van Londen, 1995	no	yes	no	yes	no
(350) Van Londen, 1991	no	yes	yes	yes	no
(351) van Son, 1995	no	no	?	yes	?
(352) van Son, 1990	no	no	yes	yes	no?
(353) Wagner, 1988	no	no	no	yes	no
(354) Waitzel, 1969	no	no	yes	yes	no
(355) Werry, 1977	no	yes	no	yes	no
(356) Werry, 1965	yes	yes	no	yes	yes
(357) Werry, 1975	no	yes	no	yes	no
(203) Whelan, 1990	yes	yes	no	yes	no
(358) Wickes, 1958	no	no	no	yes	yes
(359) Wilken-Jensen, 1959	no	yes	yes	yes	no
(360) Williams, 1978	no	yes	yes	yes	no
(361) Wood, 1994	no	yes	yes	yes	no
(362) Woodhead, 1967	no	no	no	yes	yes
(363) Yamanishi, 1988	no	yes	yes	yes	no
(364) Young, 1973	no	yes	no	yes	no
(365) Young, 1964	no	no	no	yes	no
(366) Young, 1965	no	no	no	yes	yes

Author	RCT	Comparison group	Systematic baseline	Systematic outcomes	Organic causes excluded
(367) Young, 1972	no	no	no	yes	no
(368) Young, 1972	no	yes	no	yes	yes
(369) Young, 1965	no	no	no	yes	yes

Appendix 6: Other Study Details

i) Countries of origin: number of RCTs from each country

NB Trials may be entered under more than one intervention
* = foreign language paper

	Desmopressin	Imipramine	Other drugs	Alarm	DBT	RCT	Combined	Complement
Australia	1		1	3	4			
Canada			1				1	1
Czechoslovakia	1							
Denmark	2*		1*					
Finland	2							
France		1*						
Germany		1*						
Ghana			1	1				
India		2	1					
Israel	1							
Italy	1*							
Mexico		1*						
Norway	1*	1*						
S. Africa								1
Spain	1*							
Sweden	3			1			1*	
Holland	2						1	
Turkey		1*	1*	1*				
United Kingdom		5	3	7	2	1		
USA	3	6	3	6	2	1	1	

ii) Year of Publication: number of studies published

NB Trials may be entered under more than one intervention

	Desmopressin	Imipramine	Other drugs	Alarm	DBT	RCT	Combined	Complement
1960 -64			1					
1965 -69		6	3				1	
1970 -74		6	2	5	1			
1975 -79	2		1	2	1			
1980 -84	5	1	1	3	5	1		
1985 -89	4	2	1	5	1	1	2	1
1990 -94	4	2	1	2	1			1
1995 -	3	1	2					

iii) Recruitment to Trials: number of studies

NB Trials may be entered under more than one intervention

	Desmo	Imipr	Other drugs	Alarm	DBT	RCT	Combined	Complement
Patients presenting at out-patient\enuresis clinic	2	6	4	7	4			
Residents in institution		3		2	1			
Responding to advert etc		2		3	1	2	1	2
Located by survey	1	2	1	3				
Referred specifically to study	2	2	2	4		2		
Multi-centre trial	1	2						
No details	11	4	4				2	
GPs patients			1					

Appendix 7:Quality and Reported Outcomes of Intended Studies

1 = Allocation concealment; Outcomes: 2a = mean frequency of wetting; 2b = Attainment of 14 consec dry nights; 2c = mean wetting frequency at follow-up; 2d = Relapse;; 3 = Diurnal wetting excluded; 4 = Blinding; 5 = Comparable groups at baseline; 6 = Washout phase in cross over trials; 7 = Intention to treat (include dropouts); 8 = Follow-up for at least 3 months; 9 = means and standard deviations reported where appropriate

	1	2a	2b	2c	2d	3	4	5	6	7	8	9
(73)	B	y	y	n	n	?	yy	y	na	?	n	y
(89)	B	y	n	y	n	n	yy	y	na	n	n	n
(52)	B	n	n	n	n	y	na	?	na	y	y	n
(90)	B	n	n	n	n	?	yy	?	na	?	y	n
(74)	A	y	y	y	y	?	yy	na	n	?	n	y
(123)	B	y	y	n	n	?	na	y	na	n	y	n
(124)	B	y	y	n	y	?	na	y	na	n	y	n
(114) (B)	B	y	y	n	y	?	na	n	na	y	y	g
(114) (A)	B	y	y	n	y	?	na	?	na	y	y	g
(122)	B	n	n	n	y	n?	na	n	na	?	Y	y
(75)	A	y	y	y	y	?	yy	y	na	?	y	y
(113) B	C	n	y	n	n	y	na	y	na	n	y	n
(53)	C	n	y	n	n	n	na	y	na	n	n	y
(113) (A)	C	y	y	n	y	?	na	y	na	n	y	n
(128)	B	y	n	y	n	y	na	?	na	?	y	g
(115)	B	n	y	n	n	y	na	y?	na	y	y	y
(76)	B	y	y	n	n	y	yy	?	n	n	n	n
(91)	B	y	n	n	n	?	yy	y	na	n	y	n
(116)	B	y	y	y	y	?	na	y?	na	n	n?	Y
(112)	B	y	n	n	n	n	y	na	n	n	n	n
(126)	B	y	n	y	n	y	na	?	na	?	n	g
(92)	C	y	y	n	y	?	?	y	na	?	n	y
(72)	B	y	n	y	n	y	yy	na	y?	y	n	y
(117)	B	y	y	n	n	?	na	n?	na	y?	y	g
(125)	B	y	y	n	y	y	na	y	na	y	y	g
(79)	B	y	y	n	n	?	yy	?	na	?	y	y

(93)	B	y	n	y	n	?	?	?	na	n	y	n
(94)	B	y	n	n	n	?	y	y	na	y	n	y
(95)	A	y	n	y	n	y	yy	na	y	?	y	y
(127)	B	y	n	n	n	y	n	n	na	n	n	g
(110)	A	y	y	n	n	?	yy	?	na	n	n	n
(111)	B	y	n	n	n	y	yy	na	n	n	n	n
(96)	C	n	y	n	n	?	yy	na	n	?	n	y
(97)	C	y	n	n	n	?	yy	na	n	y	y	n
(80)	B	y	y	n	n	n	yy	y	na	n	n	y
(98)	B	y	n	n	n	?	yy	y	n?	n	n	y
(81)	B	y	n	y	n	?	yy	y	na	n	n	n
(82) (A)	B	y	n	n	y	?	yy	na	?	?	y	y
(82) B	B	y	n	n	y	?	yy	na	?	?	n	y
(101)	C	y	y	y	y	?	yy	?	n	n	n	g
(205)	B	y	n	n	n	y	yy	y	na	?	y	y
(104)	C	y	n	n	n	n	yy	y	n	n	y	n
(119)	B	y	y	n	y	?	na	y	na	?	y	n
(56)	A	y	n	y	n	y	yy	na	y	y	y	y
(120)	C	n	y	n	y	n	na	?	na	n	y	n
(87)	B	y	n	n	y	y	yy	na	?	y	n	y
(86)	B	y	n	n	n	y	yy	na	n	y?	n	y
(106)	B	y	n	n	n	?	yy	na	n	n	n	n
(88)	B	y	n	n	n	?	yy	na	n	?	n	y
(121)	C	y	y	n	y	?	y?	y	na	y	y	n
(1)	B	y	n	y	y	y	na	y	na	n	y	g
(108)	B	y	n	n	n	?	yy	?	na	?	n	g

1 = Allocation concealment; Outcomes: 2a = mean frequency of wetting; 2b = Attainment of 14 consec dry nights; 2c = mean wetting frequency at follow-up; 2d = Relapse; 3 = Diurnal wetting excluded; 4 = Blinding; 5 = Comparable groups at baseline; 6 = Washout phase in cross over trials; 7 = Intention to treat (include dropouts); 8 = Follow-up for at least 3 months; 9 = means and standard deviations reported where appropriate

Appendix 8: Sensitivity Analysis

A8.1 Desmopressin

A8.1.1 Non Randomised Controlled Studies

Four of the non-randomised studies involved desmopressin (Table A8.1.1a)

Table A8.1.1a Non-randomised studies involving desmopressin

Author	Number	Intervention
Stenberg, 1994 (149)	10 crossover	A: Desmopressin tablets (titrated dosage) B: placebo tablets
Ferrie, 1984 (137)	22/25 crossover	A: intranasal desmopressin (20 µg) B: placebo
Capozza, 1991 (60)	A: 10 B: 10 C: 10 D: 10	A: Desmopressin (30 g a day) B: Acupuncture (once a week points MP6, MP10, and VC4) C: Desmopressin + acupuncture (as above) D: placebo
Evans, 1992 (136)	A: 28 B: 27	A: 1 month desmopressin nasal spray (20 g) increased to 40 g if any wet nights after the first 3 nights B: 3 month desmopressin nasal spray - dosage as above.

Comparisons with placebo are discussed in the main report (Section 6.2).

One non-randomised study compared 30 µg of desmopressin with placebo (60). There were 1.19 fewer wet nights in the desmopressin than the placebo group (absolute difference).

A non-randomised trial which used quota allocation to match the groups compared different durations of treatment with desmopressin (136). There was no significant difference in the mean number of wet nights per week when the patients were treated for either 1 month or 3 months: WMD: -0.6 (95%CI: -1.5 to 0.3) or in the number becoming totally dry: RR = 1.61(95%CI: 0.41 to 6.08).

When 30 µg desmopressin was compared with acupuncture (60) desmopressin produced 0.84 fewer wet nights (absolute difference). When desmopressin was compared with acupuncture augmented by desmopressin the combined treatment produced 1.61 fewer wet nights (absolute difference). After 4 weeks these differences were 1.54 and 2.66 respectively, the groups involving acupuncture having more dry nights per week.

A8.1.2 RCTs: No Baseline Measure of Wetting

None of the RCTs of desmopressin lacked baseline measurements of wetting.

A8.1.3 RCTs: Organic Causes Not Excluded

All of the RCTs of desmopressin had excluded organic causes of wetting. .

A8.2 Imipramine

A8.2.1 Non Randomised Controlled Studies

Six non-randomised studies, involving imipramine, which otherwise met the inclusion criteria, were located (Table A8.2.1).

Table A8.2.1 Non-randomised studies involving imipramine

Author	Number	Intervention
Laybourne, 1968 (141)	24 crossover	A: imipramine (25 mg to 50 mg depending on age B: placebo
Rapoport, 1980A (146)	20 crossover boys only	A: 10 day out-patient trial of placebo B: imipramine (75 mg) at bedtime C: methscopolamine (6 mg) at bedtime
Rapoport, 1980 B (146)	20 crossover boys only	A: 10 day out-patient trial of placebo B: imipramine (75 mg) at bedtime C: desipramine (75 mg) at bedtime
Schjetne, 1970 (148)	A: 15 B: 13	A: imipramine (25 to 50mg) B: placebo
Mariuz, 1963 (142)	23 crossover deprived boys in institution	A: imipramine: 25mg orally at bedtime B: placebo
Fisher, 1963 (138)	34 crossover learning disabled	A: imipramine 25 to 50mg at 8pm B: placebo
Esperanca, 1969 (135)	50 crossover	A: imipramine B: restricted diet - no dairy, citrus, tomato or chocolate

Comparisons with placebo are discussed in the main report (Section 6.3)

Imipramine reduced the number of wet nights per week by less than one, as compared with placebo, for patients with learning disabilities classified as severely subnormal and subnormal (138). There was no difference between imipramine or desipramine in the mean number of wet nights per week: random effects WMD: 0.00 (95% CI: -0.97 to 0.97) (146); imipramine produced significantly fewer wet nights per week than methscopalamine: random effects WMD: -1.63 (95% CI:-2.53, -0.73) (146). Those given imipramine had 1.3 fewer wet nights (absolute difference) a week than those on a restricted diet (135).

A8.2.2 RCTs: No Baseline Measure of Wetting

Ten RCTs involving imipramine but without baseline measurement of wetting were located (Table A8.2.2). Of the 4 comparisons with placebo, only one gave results in terms of change in number of wet nights per week (150), the remainder used various measures of

improvement which combined "cure" and reduction in wetting. Imipramine was found to be superior to placebo in all trials

Imipramine was found superior to amitriptyline, chlordiazepoxide clinidium and piracetam (177). No significant difference was found between imipramine and viloxazine (178) nor between imipramine and diclofenac or a combination of diclofenac and imipramine (154). Two RCTs compared imipramine with a Mozes detector (a device giving electrical "stimulation" on inappropriate micturition) (172, 174). Both imipramine and the Mozes detector were reported to demonstrate cure rates better than 15% (172) but there was no difference in the cure rate of the two treatments when results were adjusted for age (174).No significant difference in positive outcome between imipramine and hypnosis was reported (153), although hypnosis was found to be superior at follow-up. An RCT reported psychological programmes to be superior to imipramine - there was no statistical analysis.

A8.2.3 RCTs: Organic Causes Not Excluded

Seven randomised controlled trails of imipramine were found where there was no indication that organic causes for wetting had been excluded (Table A8.2.3). Interestingly, 5 of these took place in residential institutions.

With the exception of one trial involving children in a hospital for those with learning difficulties,(192), imipramine was found to be superior to placebo. Imipramine also significantly reduced the number of wet nights per week compared with emepronium (Cetiprin) (315)

Table A8.2.2 RCTs without baseline, involving imipramine

Author	Number	Interventions
Agarwala, 1968 (150)	29 crossover	A: imipramine B: placebo
Banerjee, 1993 (153)	A: 25 B: 25	A: hypnosis: variable number B: imipramine (25 mg every night)
Batislam, 1995 (154)	A: 16 B: 20 C: 30 D: 12	A: imipramine B: Diclofenac Na C: imipramine + diclofenac D: placebo
Friday, 1966 (163)	A: 22 B: 29	A: imipramine B: placebo:
Iester, 1991 (166)	A: 36 B: 36 C: 96	A: 6 weeks with imipramine B: 3 step programme: a) reassurance to parents; b) bladder retention training and wakening before micturition; c) parental involvement C: motivational therapy (counselling + computer programme) + 3 step therapy
Khorana, 1972 (168)	A: 50 B: 50	A: imipramine hydrochloride (25mg or more) B: placebo
McKendry, 1975 (172)	A: 73 B: 74 C: 75	A: Restricted diet B: imipramine C: mozes Detector
Netley, 1984 (174)	A: 31 B: 31	A: imipramine hydrochloride B: mozes Detector
Yurdakok, 1986 (177)	A: 14 B: 8 C: 10 D: 9	A: imipramine B: amitriptyline C: chlordiazepoxide clinidium D: piracetam
Yurdakok, 1987 (178)	A: 21 B: 16	A: 25mg imipramine before bedtime B: 50 mg viloxazine before bedtime

Table A8.2.3 RCTs of imipramine: organic causes not excluded

Author	number	intervention
Drew, 1966 (181)	28 children's home	A: imipramine B: placebo
Harrison, 1970 (184)	A: 30 B: 32 single sex orphanages	A: imipramine B: placebo for 20 nights
Milner, 1968 (189)	n = 212 Long stay psychiatric patients	A: desipramine - 75mg B: imipramine - 75mg C: nortriptyline - 75 mg D: placebo
Petersen, 1974 (315)	61/69 crossover	A: imipramine B: imipramine N oxide C: emepronium (cetiprin) D: placebo
Treffert, 1964 (191)	9 children in psychiatric hospital	A: Imipramine B: placebo
Valentine, 1968 (192)	n = 16 hospital for children with learning difficulties	A: Imipramine B: placebo

A8.3 Other Drug Comparisons

A8.3.1 Non Randomised Controlled Studies

The other non-randomised drug comparisons involved substances not reported in RCTs. Besides the study discussed above (146) there were 5 additional studies (Table A8.3.1).

As seen above (A8.2.1) desipramine and imipramine were equally effective in reducing the mean number of wet nights per week (146) but methscopalamine was less effective than imipramine (146). Patients given diclofenac suppositories had significantly fewer wet nights per week than those given glycerol suppositories: random effects WMD: -1.9 (95% CI: -2.4, -1.4) (143). This was sustained at 1 and 2 month follow-ups: WMD: -2.1 (95% CI: -2.6, -1.6) and WMD = -2.8 (95% CI: -3.1 to - 2.5) respectively (143). Patients given emepronium bromide had 0.46 (absolute difference) fewer wet nights per week than those given placebo (140). Other non-RCTs investigated different doses of Human Chorionic Gonadotrophin (132) but the results of the two groups were combined; propiverin (Mictretten) (144, 145) - in the first of the trials the results were not given by treatment group; in the second there were no results for the placebo group.

Table A8.3.1: Non randomised trials involving other drugs

Author	Number	Intervention
Metin, 1992 (143)	A: 24 B: 14	A: diclofenac sodium (Voltaren) suppositories 100mg a night B: glycerol suppositories
De Jonge, 1973 (132)	A: 10 B: 9	A: human chorionic gonadatrophin ("Pregnyl") - 500iu three times a week - intramuscular (total 7500iu) B: human chorionic gonadotrophin - 1000iu twice weekly (total 10000iu)
Jensen, 1982 (140)	23 crossover	A: emepronium bromide B: placebo
Nentwich, 1986 (144)	A: 19 B: 9	A: propiverin (Mictoretten) B: placebo
Otto-Unger, 1985 (145)	A: 26 B: 10	A: propverinhydrochloride (Mictoretten) B: placebo

A8.3.2 RCTs: No Baseline Measure of Wetting

A wide variety of drugs were investigated in RCTs which lacked systematic measurement of baseline wetting. Fourteen trials, in addition to those discussed above (154, 177, 178) were found (Table A8.3.2)

Three RCTs compared amitriptyline with placebo (175, 294, 329): all found amitriptyline significantly better at reducing wetting. In addition, amitriptyline was reported to have better results than piracetam and be equally effective as chlordiazepoxide clinidium although imipramine was found to be significantly superior to all three (177). Amitriptyline initially performed better than either "psychological" methods alone (waking and use of a chart) or a combination of psychological methods and amitriptyline (173); however, the combined method had better results at follow-up. A combination of chlordiazepoxide (5mg) and amitriptyline (12.5mg) was superior to placebo in terms of the number 50% improved or more (161).

One RCT found indomethacin suppository resulted in 3.7 fewer wet nights per week than placebo (absolute difference) (151). Both diclofenac sodium and a combination of imipramine and diclofenac sodium were reported to be significantly superior to placebo: there was no difference between the drugs in effectiveness (154). Both amphetamine sulphate and posterior pituitary snuff were reported to perform better than placebo (165). However the amphetamine kept the children awake. Diazepam was reported to produce significantly better results than placebo (170). No significant difference between viloxazine and imipramine was reported (178). Oxybutynin produced a statistically significant decrease in wet nights compared with dicyclomine (171) (370). Two RCTs compared propantheline with placebo (165, 176); neither found a significant difference between the conditions. No difference was found between a combination of propantheline and phenobarbitone and placebo or with propantheline alone (176). Neither hydroxyzine hydrochloride (a tranquillizer) nor methylphenidate hydrochloride (Ritalin - a stimulant) were found superior to placebo (155). No significant difference between meprobamate or placebo was reported (156). No significant difference between trimipramine and placebo was reported (162). No significant difference between piracetam and placebo was reported (169) cf (177) above.

Table A8.3.2 RCTs of other drugs: no baseline measure of wetting

	Number	Intervention
al-Waili, 1989 (151)	19 crossover	A: indomethacin suppository B: placebo
Breger, 1962 (155)	A: 50 B: 50 C: 50	A: hydroxyzine hydrochloride B: methylphenidate hydrochloride (Ritalin) C: placebo
Breger, 1961 (156)	A: 50 B: 50	A: meprobamate (3 times a day; dosage depends on age) B: identical placebo
Forsythe, 1972 (162)	A: 121 B: 120	A: increasing dose trimipramine B: identical placebo in corresponding dosages
Forsythe, 1972 (161)	A: 121 B: 129	A: chlordiazepoxide (5mg) + amitriptyline (12.5mg) B: placebo
Holt, 1956 (165)	40 crossover	A: propantheline ("Probanthine") - 60mg at bedtime B: amphetamine sulphate (10mg at bedtime) C: posterior-pituitary snuff ("Di-sipidin") D, E, F: corresponding placebos
Wallace, 1969 (176)	A: 100 B: 100 C: 100	A: propantheline (3 x 15 mg) B: 3 x 15mg propantheline + 15mg phenobarbitone C: 3 x placebo tablets
Khosroshahi, 1989 (169)	A: 18 B: 15 C: 12 D: 14 E: 14	A: 20mg/kg Piracetam at bedtime B: psychotherapy: C: drug and psychotherapy D: single dose placebo at bedtime E: EPILEPTICS: diphenylhydantoin 5mg/kg/day
Kline, 1968 (170)	A: 28 B: 22	A: diazepam 5mg B: placebo
Marconi, 1984 (171) (370)	A: 18 B: 16	A: oxybutynin 5mg three times a day B: diciclomime: 20mg 3 times a day
Lines 1968 (294)	36 crossover	A: amitriptyline B: placebo
Mehrotra, 1980 (173)	A: 20 B: 20 C: 20	A: amitriptyline (10mg - 50mg) B: "psychological" and amitriptyline C: "psychological" - waking to void and use of chart
Poussaint, 1966 (175)	A: 9 B: 9	A: amitriptyline B: placebo
Shah 1971 (329)	20 crossover children with behaviour problems	A: amitriptyline B: placebo

A8.3.3 RCTs: Organic Causes Not Excluded

Three additional RCTs involving other drugs but lacking proper procedures to exclude organic causes of bed wetting were located (Table A8.3.3). Other studies have already been discussed (189, 315)

Table A8.3.3 RCTs involving other drugs: organic causes not excluded

Author	numbers	intervention
General Practitioner Research Group, 1970 (182)	55 crossover	A: triclofos B: ephedrine
Lake, 1968 (290)	A: 25 B: 2	A: nortriptyline B: placebo
Leys, 1956 (187)	A: 33 B: 32	A: propantheline bromide B: placebo

Two RCTs compared nortriptyline with placebo (189, 290) - both favoured nortriptyline. Desipramine was also reported to be significantly superior to placebo (189) in adult psychiatric patients. The results of the trial comparing propantheline with placebo were unclear (187). No significant difference was found between triclofos and ephedrine (182). There was no difference in the number of wet nights per week for emepronium and placebo (315)

A8.4 Alarms

A8.4.1 Non Randomised Controlled Studies

Four additional alarm studies are included in the sensitivity analysis (Table A8.4.1)

Table A8.4.1 Non randomised controlled studies involving enuresis alarms

Author	numbers	intervention
De Leon, 1966 (133)	A: 56 B: 13 C: 18	A: enuresis alarm : pad and buzzer B: psychotherapy-counselling C: no treatment control
Ronen, 1992 (147)	A: 20 B: 19 C: 20 D: 18	A: Cognitive-Behavioural Intervention B: Enuresis alarm C: Token economy D: control group
Fordham, 1989 (139)	A: 27 B: 29	A: bed based bell and pad B: pants based sensor and mini-alarm
Bradbury, 1995 (131)	A: 36 B: 35	A: Choice of bed alarm or mini-alarm + 40mcg desmopressin B: Choice of bed alarm or mini alarm

Comparisons with no treatment control are discussed in the main report (Section 6.4).

Studies that were not RCTs compared the effectiveness of several other interventions with alarm. Alarm treatment resulted in fewer wet nights per week than token economy: WMD -0.97 (95% CI: -1.78, -0.16) but there was no difference between alarm and the cognitive behavioural intervention: WMD: 0.0 (95% CI: -0.66, 0.66) (147). Alarms were also 5 times more likely to result in 14 consecutive dry nights than psychotherapy: RR: 5.11 (95% CI: 1.4 to 18.4) (133).

A8.4.2 RCTs Without Baseline Measures of Wetting

Four of these RCTs evaluated behavioural devices not used in the United Kingdom - the Mozes Detector and Uristop device (Table A8.4.2). These devices administer "electrical stimulation" to the child when inappropriate wetting occurs.

Alarm treatment was reported to be superior to either wake up treatment or control (152). The louder alarm was more effective (160), especially with children classed as slow responders. Two RCTs evaluated Uristop devices (159, 164). Neither trial found this device better than spontaneous recovery rates. The Mozes Detector did produce cure rates better than spontaneous recovery rates (172, 174). No difference was found between enuresis alarm plus methedrine and alarm alone in people with learning difficulties (167)

Table A8.4.2 RCTs: no baseline measure of wetting

Author	Numbers	Intervention
Baker, 1969 (152)	A: 10 B: 10 C: 10	A: alarm B: wake-up treatment C: waiting list control
Elinder, 1985 (159)	A: 36 B: 17	A: functioning uristop device B: non - functioning uristop
Finley, 1977 (160)	A: 10 B: 10	A: enuresis alarm (105dB bell) B: enuresis alarm (80 dB bell)
Hojsgaard, 1979 (164)	A: 32 B: 30	A: uristop device B: no treatment
McKendry, 1975 (172)	A: 73 B: 74 C: 75	A: restricted diet B: imipramine C: Mozes Detector
Netley, 1984 (174)	A: 31 B: 31	A: imipramine hydrochloride B: Mozes Detector
Kennedy, 1968 (167)	A: 3 B: 5 residential training centre for people with learning difficulties.	A: alarm + methedrine B: alarm

A8.4.3 RCTs: Organic Causes Not Excluded

Five RCTs involving alarms, where organic causes had not been eliminated were found (Table A8.4.3).

The alarm reduced wetting in comparison with control in all cases (179, 185, 188, 190). In addition this was accompanied by significant positive changes for the alarm group in school performance, physical appearance and popularity as measured by the Piers Harris Self Concept Scale (190). One trial found immediate alarms superior to delayed alarms - the latter being no more effective than control (188); a trial in a residential centre for people with learning disabilities found delayed and immediate alarms gave similar results (183) and were superior to a yoked alarm schedule not contingent on wetting. Alarm treatment and Stop-Start Training (sphincter muscle exercises) were found similarly effective (179)

Table A8.4.3: RCTs involving alarms: no medical

Author	Numbers	Intervention
Bennett, 1985 (179)	A: 9 B: 12 C: 10 D: 9	A: pad and buzzer training - alarm B: Stop-Start Training (sphincter muscle exercises) C: Dry Bed Training D: waiting list control
Hanson, 1988 (183)	n = 27 Residential Centre for people with learning difficulties	A: immediate alarm B: delayed alarm C: yoked schedule awakenings
Houts, 1986 (185)	A: 15 B: 15 C: 15 D: 11	A: enuresis alarm + retention control training + Over learning (Full Spectrum Home Training Package) B: enuresis alarm + retention control training C: enuresis alarm D: waiting list control
Lynch, 1984 (188)	A: 20 B: 20 C: 20	A: enuresis alarm - immediate B: enuresis alarm - 3 minute delay C: control
Moffatt, 1987 (190)	A: 66 B: 55	A: enuresis alarm B: waiting list control

A8.5 Multi Component Behavioural Programmes

A8.5.1 Non randomised controlled studies

Two non-RCTs looked at Dry Bed Training (Table A8.5.1)

Table A8.5.1 Non randomised controlled studies: Multi component behavioural programmes

Author	Number	Intervention
Nettelbeck, 1979 (71)	A: 7 B: 9 C: 8	A: Dry Bed Training with therapist B: Dry Bed Training with therapist but WITHOUT enuresis alarm C: no treatment control
Doleys, 1977 (134)(360)	A: 10 B: 9	A: Dry Bed Training B: retention control training

Dry Bed Training (DBT) with an alarm produced 5 fewer wet nights per week than control: WMD: -5.09 (95% CI: -6.5 to -3.7), whereas DBT without an alarm resulted in 2 fewer wet nights per week: WMD: -2.1 (95%CI: -4.1 to -1.5) (71). Comparing the two DBT conditions, use of an alarm resulted in nearly 3 fewer wet nights per week: WMD: -2.99 (95% CI: -4.4 to -1.5). DBT resulted in 5 (absolute difference) fewer wet nights per week than retention control training (134, 360).

A8.5.2 RCTs: No Baseline Measure of Wetting

One RCT which did not have a systematic baseline was found which investigated a multidimensional behavioural treatment (Table A8.5.2) This was a three step therapeutic programme involving reassurance to parents, bladder retention training and wakening before micturition and parental involvement (166). The addition of motivational therapy using counselling and a computer programme was also studied.

Table A8.5.2 RCTs: no baseline measure of wetting

Author	Numbers	Intervention
Iester, 1991 (166)	A: 36 B: 36 C: 96	A: 6 weeks with imipramine B: 3 step therapeutic programme C: motivational therapy + 3 step therapy

The behavioural therapies were reported to give better results than imipramine but there was no statistical analysis.

A8.5.3 RCTs: Organic Causes Not Excluded

Inclusion of RCTs where there had been no medical to exclude organic causes of wetting allowed investigation of Full Spectrum Home Training - a package involving use of an enuresis alarm, retention control training and over learning (185). Brief details of this and the other studies are given in Table A8.3.3

Although Dry Bed Training was found superior to control (179) both of the trials comparing Dry Bed Training with alarm found no difference between the treatments (179, 180). Full Spectrum Home Training (FSHT), alarm plus retention control training and alarm alone were initially all found to be more effective than control, with no difference between conditions (185). However, there were fewer relapses in the full FSHT package than in the other two conditions. Live training for FSHT was superior to video training (186).

Table A8.5.3 RCTs: organic causes not excluded

Author	Numbers	Intervention
Bennett, 1985 (179)	A: 9 B: 12 C: 10 D: 9	A: pad and buzzer training - alarm B: stop-start training (sphincter muscle exercises) C: dry bed training D: waiting list control
Caceres, 1982 (180)	A: 7 B: 7	A: enuresis alarm B: Dry Bed Training
Houts, 1986 (185)	A: 15 B: 15 C: 15 D: 11	A: Full Spectrum Home Training Package (FSHT) B: enuresis alarm + retention control training C: enuresis alarm D: waiting list control
Houts, 1987 (186)	A: 10 B: 10 C: 10 D: 10 A: 12 B: 12	Study 1: A: immediate live delivery of FSHT B: immediate filmed delivery of FSHT C: baseline recording + live delivery FSHT D: baseline recording + filmed delivery of FSHT Study 2 A: immediate live delivery of FSHT B: immediate filmed delivery of FSHT

A8.6 Other

A8.6.1 Non Randomised Controlled Studies

The inclusion of the non-RCTs allows several other interventions to be considered: acupuncture (60); cognitive behavioural intervention (147); token economy (147); chiropractic (66) and psychotherapy (133) (Table A8.6.1)

The cognitive behavioural intervention, token economy and chiropractic all produced significantly fewer wet nights than control. There was no significant difference in the relative risk of attaining 14 consecutive wet nights or relapsing between psychotherapy and control.

Table A8.6.1 Non randomised controlled studies of other interventions

Author	Numbers	Intervention
Capozza, 1991 (60)	A: 10 B: 10 C: 10 D: 10	A: desmopressin (30 g a day) B: acupuncture (once a week points MP6, MP10, and VC4) C: desmopressin + acupuncture (as above) D: placebo
De Leon, 1966 (133)	A: 56 B: 13 C: 18	A: enuresis alarm : pad and buzzer B: psychotherapy-counselling C: no treatment control
Ronen, 1992 (147)	A: 20 B: 19 C: 20 D: 18	A: cognitive-behavioural intervention B: enuresis alarm C: token economy D: control group
Reed, 1994 (66)	A: 36 B: 21	A: chiropractic adjustment B: sham adjustment

A8.6.2 RCTs: no baseline measure of wetting

Author	Numbers	Intervention
Banerjee, 1993 (153)	A: 25 B: 25	A: hypnosis: number of sessions depended on child B: imipramine (25 mg every night)
Cupalova, 1988 (157)	A: 25 B: 25	A: 10 real faradizations then 10 placebo faradizations B: 10 placebo faradizations then 10 real faradizations
Khosroshahi, 1989 (169)	A: 18 B: 15 C: 12 D: 14 E: 14	A: 20mg/kg Piracetam at bedtime B: psychotherapy: C: drug and psychotherapy D: single dose placebo at bedtime E: EPILEPTICS: diphenylhydantoin 5mg/kg/day
McKendry, 1975 (172)	A: 73 B: 74 C: 75	A: restricted diet B: imipramine C: mozes Detector
Mehrotra, 1980 (173)	A: 20 B: 20 C: 20	A: "psychological" - waking to void and use of chart B: amitriptyline (10mg - 50mg) C: "psychological" and amitriptyline

A8.6.2 RCTs: No Baseline Measure of Wetting

Consideration of the RCTs without systematic measurement of baseline wetting allowed hypnosis (153); faradization (157); psychotherapy (169); diet (172) and psychological methods (star chart) (173) to be investigated (Table A8.6.2)

No significant difference was found in positive outcome between imipramine and hypnosis, although the hypnosis results were superior at follow-up (153). No difference was found between real and placebo faradizations (157). No evidence was found to suggest that there was any benefit to restricting diet (172). Waking and the use of a star chart was initially more effective than amitriptyline (173).

A8.6.3 RCTs: Organic Causes Not Excluded

No randomised controlled trials where organic causes were not excluded were found which investigated other treatments.

REFERENCES

1. Wille S. Comparison of desmopressin and enuresis alarm for nocturnal enuresis. Archives of Disease in Childhood 1986;61(1):30-3.
2. WHO. F 98.0 Nonorganic enuresis. In: WHO, ed. The ICD-10 classifcation of mental and behavioural disorders: Clinical descriptions and diagnostic Guidelines. Geneva: WHO, 1992:
3. American Psychiatric Association. 307.60 Functional Enuresis. In: APA, ed. Diagnostic and Statistical Manual of Mental Disorders. 3rd edition. Revised ed.
4. Blackwell C. A guide to enuresis: A guide to treatment of enuresis for professionals. Bristol: ERIC, 1989.
5. Jarvelin MR, Huttunen NP, Seppanen J, Seppanen U, Moilanen I. Screening for urinary tract abnormalities among day and night wetting children. Scandinavian Journal of Urology and Nephrology 1990;24(3):181 -189.
6. Hjalmas K. Functional daytime incontinence: definitions and epidemiology. Scandinavian Journal of Urology and Nephrology 1992;141:39-44.
7. Jarvelin MR. Developmental history and neurological findings in enuretic children. Developmental Medicine and Child Neurology 1989;31:728-736.
8. Djurhuus JC, Norgaard JP, Rittig S. Monosymptomatic bed wetting. Scandinavian Journal of Urology and Nephrology 1992;141:7-9.
9. de Jonge GA. Epidemiology of enuresis: A survey of the literature. In: Kolvin I, MacKeith RC, Meadow SR, eds. Bladder control and enuresis. London: William Heinemann Medical Books, 1973:
10. Krantz I, Jykas E, Ahlberg BM, Wedel H. On the epidemiology of nocturnal enuresis - a critical review of methods used in descriptive epidemiological studies on nocturnal enuresis. Scandinavian Journal of Urology and Nephrology Suppl 1994;163:75-82.
11. Diagnostic Steering Committee of the American Sleep Disorders Association. Sleep Enuresis: 780.56-0. The International Classification of Sleep Disorders Diagnostic and Coding Manual. 1990:
12. Verhulst FC, van der Lee JH, Akkerhuis GW, Sanders Woudstra JA, Timmer FC, Donkhorst ID. The prevalence of nocturnal enuresis: do DSM III criteria need to be changed. A brief research report. Journal of Child Psychology and Psychiatry and Allied Disciplines 1985;26(6):989-893.
13. Rutter M, Yule W, Graham P. Enuresis and behavioural Deviance: Some Epidemiological Considerations. In: Kolvin I, MacKeith RC, Meadow SR, eds. Bladder control and enuresis. London: William Heinemann Medical Books, 1973:
14. Morgan R. The treatment of enuresis amongst child clients of a social services Department. British Journal of Social Work ;9(2):217-231.
15. Butler. Pilot study: nocturnal enuresis and the homeless. 1997: Personal Communication.
16. Forsythe WI, Redmond. Enuresis and spontaneous cure rates: a study of 1129 enuretics. Archives of Disease in Childhood 1974;49:259-263.
17. Essen J, Peckham C. Nocturnal enuresis in childhood. Developmental Medicine and Child Neurology 1976;18:577-589.

18. Devlin JB. Prevalence and risk factors for childhood nocturnal enuresis. Irish Medical Journal 1991;84(4):118-120.
19. Bakwin H. Enuresis in twins. American Journal of Diseases of Childhood? 1971;121:222-225.
20. Bakwin H. The genetics of enuresis. In: Kolvin I, MacKeith RC, Meadow SR, eds. Bladder control and enuresis. London: William Heinemann Medical Books, 1973:
21. Eiberg H et al. Assignment of dominant inherited nocturnal enuresis (ENURI). Nature Genetics 1995;10:354-356.
22. Norgaard JP, Djurhuus JC. The pathophysiology of enuresis in children and young adults. Clinical Pediatrics 1993;32 special issue(July):5-9.
23. Mikkelsen EJ, Rapoport JL. Enuresis: psychopathology, sleep stage, and drug response. Urologic Clinics of North America 1980;7(2):361-77.
24. Koff SA. Why is desmopressin sometimes ineffective in curing bed wetting?? Scandinavian Journal of Urology and Nephrology Suppl 1996;173:103-107.
25. Doleys DM. Behavioural treatment for nocturnal enuresis: a review of recent literature. Psychological Bulletin 1977;84:30-54.
26. MacKeith RC. Is maturational delay a frequent factor in theorigins of primary nocturnal enuresis? Developmental Med. Child. Neurol 1972;14:217 - 223.
27. Houts AC. Nocturnal enuresis as a biobehavioral problem. Behaviour Therapy 1991;22:133-151.
28. Shaffer D. Enuresis. In: Rutter MaH, L, ed. Child Psychiatry: Modern Approaches. Oxford: Blackwell Scientific Publications, 1977:
29. Moffatt ME. Nocturnal enuresis: psychologic implications of treatment and non-treatment. Journal of Pediatrics 1989;114 (4)(2):697-704.
30. Maizels M, Gandhi K, Keating B, Rosenbaum D. Diagnosis and treatment for children who cannot control urination. Current Problems in Pediatrics 1993;23(10):402-450.
31. Fergusson DM, Horwood LJ. Nocturnal enuresis and behavioural problems in adolescence: A fifteen year longitudinal study. Pediatrics 1994;94(5):662-668.
32. Mark SD, Frank JD. Nocturnal enuresis. British Journal of Urology: 1995;75(4):427-34.
33. Fitzwater D, Macknin ML. Risk/benefit ratio in enuresis therapy. Clinical Pediatrics 1992;May:308-310.
34. Warzak WJ. Psychosocial implications of nocturnal enuresis. Clinical Pediatrics 1992;Special edition:38 - 40.
35. Moffatt M. Nocturnal enuresis- is there a rationale for treatment. Scandinavian Journal of urology and Nephrology Suppl 1994;163:55-66.
36. Butler RJ. Nocturnal enuresis. The child's experience. Oxford: Butterworth-Heinemann Ltd., 1994.
37. Meadow SR. Management of nocturnal enuresis. In: Meadow SR, ed. Desmopressin in enuresis. Proceedings of an International Symposium held at the Royal College of Physicians. London: Horus Medical Publications, 1988:
38. Butler RJ, Redfern EJ, Holland P. Children's notions about enuresis and the implications for treatment. Scandinavian Journal of Urology & Nephrology. Supplementum: 1994;163:39-47.
39. Morgan R. Guidelines in the minimum standards of practice in the treatment of enuresis. Bristol, ERIC 1993:
40. Djurhuus JC, Norgaard JP, Hjalmas K, Wille S. Nocturnal enuresis. A new strategy for treatment against a physiological background. Scandinavian Journal of Urology and Nephrology Suppl 1992;143:3-29.

41. Harris AB. Clinical experience with desmopressin: efficacy and safety in central diabetes insipidus and other conditions. Journal of Pediatrics 1989;114 4(2):711-718.
42. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. 1996;No 32(September 1996).
43. Hjalmas K, Bengtsson B. Efficacy, safety and dosing of desmopressin for nocturnal enuresis in Europe. Clinical Pediatrics 1993;32 Special Issue:25-30.
44. Robson W, Norgaard J, Leung A. Hyponatraemia in patients with nocturnal enuresis treated with desmopressin. European Journal of Pediatrics 1996;155:959 - 962.
45. Warzak WJ, Friman PC. Current concepts in Pediatric Primary Nocturnal Enuresis. Child and Adolescent Social Work Journal 1994;11(6):507-523.
46. British Medical Association. British National Formulary. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1997. vol 33).
47. Rushton HG. Older pharmacologic therapy for nocturnal enuresis. [Review]. Clinical Pediatrics 1993;Spec No: 10-3.
48. Parkin JM, Fraser MS. Poisoning as a complication of enuresis. Developmental medicine and Child Neurology 1972;14:727 - 730.
49. Stewart MA. Treatment of Bed wetting. JAMA 1975;232(3):281-283.
50. Forsythe WI, Butler RJ. Fifty years of enuretic alarms: a review of the literature. Archives of Disease in Childhood 1989;64:879-885.
51. Howe AC, Walker CE. Behavioural management of toilet training, enuresis and encopresis. Pediatric Clinics of North America 1992;39(3):413-432.
52. Azrin NH, Sneed TJ, Fox RM. Dry-bed: a rapid method for eliminating bed wetting (enuresis) in the retarded. Behaviour, Research and Therapy 1973;11:427-434.
53. Butler RJ, Brewin CR, Forsythe WI. A comparison of two approaches to the treatment of nocturnal enuresis and the prediction of effectiveness using pre-treatment variables. Journal of Child Psychology & Psychiatry & Allied Disciplines 1988;29(4):501-9.
54. Houts AC, Liebert RM, Padawer W. A delivery system for the treatment of primary enuresis. Journal of Abnormal Child Psychology 1983;11(4):513-519.
55. Mishne JM. Primary nocturnal enuresis: a psychodynamic clinical perspective. Child and Adolescent Social Work Journal 1993;10(6):469-495.
56. Sukhai RN, Mol J, Harris AS. Combined therapy of enuresis alarm and desmopressin in the treatment of nocturnal enuresis. European Journal of Pediatrics 1989;148(5):465-7.
57. Novello AC, Novello R. Enuresis. Pediatric Clinics of North America 1987;34:719-733.
58. Sorotzkin B. Nocturnal enuresis: Current perspectives. Clinical Psychology Review 1984;4:293-317.
59. Bartocci C, Lucentini M. [Acupuncture and micro-massage in the treatment of idiopathic nocturnal enuresis]. [Italian]. Minerva Medica 1981;72(33):2237.
60. Capozza N, Creti G, De Gennaro M, Minni B, Caione P. [The treatment of nocturnal enuresis. A comparative study between desmopressin and acupuncture used alone or in combination]. [Italian]. Minerva Pediatrica 1991;43(9):577-82.
61. Minni B, Capozza N, Creti G, De Gennaro M, Caione P, Bischko J. Bladder instability and enuresis treated by acupuncture and electro-therapeutics: early urodynamic observations. International Journal of Acupuncture and Electrotherapeutics Research 1990;15:19-25.
62. Roje-Starcevic M. The treatment of nocturnal enuresis by acupuncture. Neurologija 1990;39(3):179-184.
63. Tuzuner F, Kecik Y, Ozdemir S, Canakci N. Electro-acupuncture in the treatment of enuresis nocturna. Acupuncture & Electro-Therapeutics Research ; 1989;14(3-4):211-5.

64. Gemmell HA, Jacobson BH. Chiropractic management of enuresis: time series descriptive design. Journal of Manipulative and Physiological Therapeutics 1989;12(5):386-389.
65. Johnson HH. Chiropractic care of children with nocturnal enuresis: a prospective outcome study [letter; comment]. Journal of Manipulative & Physiological Therapeutics 1991;14(8):485-7.
66. Reed WR, Beavers S, Reddy SK, Kern G. Chiropractic management of primary nocturnal enuresis. Journal of Manipulative & Physiological Therapeutics 1994 1994;Nov-17(9):596-600.
67. Stanton HE. Enuresis, homoeopathy, and enhancement of the placebo effect. American Journal of Clinical Hypnosis 1981;24(1):59-61.
68. Butler RJ. Establishment of working definitions in nocturnal enuresis. Archives of Disease in Childhood 1991;66:267-271.
69. Butler RJ, Brewin CR, Forsythe WI. Relapse in children treated for nocturnal enuresis: prediction of response using pre-treatment variables. Behavioural Psychotherapy 1990;18:65-72.
70. Houts AC, Berman JS, Abramson H. Effectiveness of psychological and pharmacological treatments for nocturnal enuresis. Journal of Consulting & Clinical Psychology 1994;62(4):737-45.
71. Nettelbeck T, Langeluddecke P. Dry bed training without an enuresis machine. Behaviour Research and Therapy 1979;17(4):403-404.
72. Janknegt RA, Smans AJ. Treatment with desmopressin in severe nocturnal enuresis in childhood. British Journal of Urology 1990;66(5):535-7.
73. Aladjem M, Wohl R, Boichis H, Orda S, Lotan D, Freedman S. Desmopressin in nocturnal enuresis. Archives of Disease in Childhood 1982;57(2):137-40.
74. Birkasova M, Birkas O, Flynn MJ, Cort JH. Desmopressin in the management of nocturnal enuresis in children: a double-blind study. Pediatrics 1978;62(6):970-4.
75. Burke JR, Mizusawa Y, Chan A, Webb KL. A comparison of amitriptyline, vasopressin, and amitriptyline with vasopressin in nocturnal enuresis. Pediatric Nephrology 1995;9(4):438-440.
76. Fjellestad-Paulsen A, Wille S, Harris AS. Comparison of intranasal and oral desmopressin for nocturnal enuresis. Archives of Disease in Childhood 1987;62(7):674-7.
77. Holt J, Borresen B. [Enuresis nocturna in school children in Bodo. A therapeutic trial with a vasopressin analog: desmopressin and imipramine]. [Norwegian]. Tidsskrift for Den Norske Laegeforening 1986;106(8):651-4.
78. Janknegt R, Zweers H, Delaere K, Kloet A, Khoe S, Arendson H. Oral desmopressin as a new treatment modality for primary nocturnal enuresis in adolescents and adults: a double-blind randomised, multicentre study. The Journal of Urology 1997;157:513 - 517.
79. Kjoller SS, Hejl M, S PP. [Enuresis treated with minurin. DDAVP). A controlled clinical study]. [Danish] 1984;Ugeskrift for Laeger(146):43.
80. Martin Hernandez E, Fernandez Ovies JM, Guzman-Guzman A, Alvarez Aldean J, Barrio Corrales F. Clinical effectiveness and safety of desmopressin in the treatment of infantile enuresis. Rev Esp Pediatr 1993;49(294):497-501.
81. Miller K, Klauber GT. Desmopressin acetate in children with severe primary nocturnal enuresis. Clinical Therapeutics 1990;12(4):357-366.
82. Post EM, Richman RA, Blackett PR, Duncan KP, Miller K. Desmopressin response of enuretic children. Effects of age and frequency of enuresis. American Journal of Diseases of Children 1983;137(10):962-3.

83. Rittig S, Knudsen UB, Sorensen S, Djurhuus JC, Norgaard JP. Long term double-blind cross over study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadow SR, ed. Desmopressin in enuresis. Proceedings of an International Symposium held at the Royal College of Physicians. London: Horus Medical Publications, 1988:43-55.
84. Rushton HG, Belman AB, Zaontz M, Skoog SJ, Sihelnik S. Response to desmopressin as a function of urine osmolality in the treatment of monosymptomatic nocturnal enuresis: a double-blind prospective study. Journal of Urology : 1995;154(2 Pt 2):749-53.
85. Segni G, Salvaggio E, Parenti D, Cataldi L, Auriti C, Rossodivita A. New therapeutic prospect in enuresis: desmopressin (DDAVP). [Italian]. Minerva Pediatrica 1982;34(1-2):45-52.
86. Terho P, Kekomaki M. Management of nocturnal enuresis with a vasopressin analogue. Journal of Urology 1984;131(5):925-7.
87. Terho P. Desmopressin in nocturnal enuresis. Journal of Urology 1991;145(4):818-20.
88. Tuvemo T. DDAVP in childhood nocturnal enuresis. Acta Paediatrica Scandinavica 1978;67(6):753-5.
89. Attenburrow AA, Stanley TV, Holland RP. Nocturnal enuresis: a study. Practitioner 1984;228(1387):99-102.
90. Bindelglas PM, Dee GH, Enos FA. Medical and psychosocial factors in enuretic children treated with imipramine hydrochloride. American Journal of Psychiatry 1968;124:1107-.
91. Fournier J-P, Garfinke BD, Bond A, Beauchesne H. Pharmacological and behavioural management of enuresis. Journal of the American Academy of Child and Adolescent Psychiatry 1987;26(6):849-853.
92. Ingle VN, Panase V. Enuresis - a comparative study of imipramine and tranquilizers in its management. Indian Pediatrics 1968;5:222-225.
93. Kolvin I, Taunch J, Currah J, Garside RF, Nolan J, Shaw WB. Enuresis: a descriptive analysis and a controlled trial. Developmental Medicine and Child Neurology 1972;14(6):715-726.
94. Kumazawa-Ichikawa MR, Franco-Tostado B, Ruvalcaba-Aceves R. [Management of primary nocturnal enuresis in school children with slow learning ability: usefulness of imipramine]. [Spanish]. Boletin Medico del Hospital Infantil de Mexico 1990;47(6):390-4.
95. Kunin SA, Limbert DJ, Platzker AC, McGinley J. The efficacy of imipramine in the management of enuresis. Journal of Urology 1970;104(4):612-615.
96. Manhas RS, Sharma JD. Tofranil (imipramine) in childhood enuresis: a controlled clinical trial of Tofranil (imipramine) in the treatment of 72 cases of childhood enuresis in Kashmir. Indian Practitioner 1967;66:663-669.
97. Martin GI. Imipramine pamoate in the treatment of childhood enuresis: A double blind study. American Journal of Diseases in Children 1971;122(1):42-47.
98. Maxwell C, Seldrup J. Imipramine in the treatment of childhood enuresis. Practitioner 1971;207:809-814.
99. Moltke H, Verder H. [Enuresis nocturna. A double-blind study with furosemide, imipramine and placebo]. [Danish]. Ugeskrift for Laeger 1979;141(21):1399-401.
100. Motavalli N, Tuzun U, Tuna S, Yargic I, Aydogmus K. Comparison of the effectiveness of three different treatment modalities in enuresis nocturna. Noropsikiyatri Arsivi 1994;31(3):146-150.
101. Poussaint AF, Ditman KS. A controlled study of imipramine (Tofranil) in the treatment of childhood enuresis. The Journal of Pediatrics 1965;67:283-290.

102. Roy JY, Colard R, Tetreault L. Psychopharmacological aspects of the use of imipramine in enuresis in 26 deaf mutes [French]. Union Medicale du Canada 1970;99(8):1420-1427.
103. Schroder G, Fliessbach R. [A controlled trial with Tofranil mite in the treatment of 62 enuretic patients]. Mschr. Kinderheilk 1971;119(4):148-151.
104. Shaffer D, Costello AJ, Hill ID. Control of enuresis with imipramine. Archives of Disease in Childhood 1968;43(232):665-671.
105. Smellie JM, McGrigor VS, Meadow SR, Rose SJ, Douglas MF. Nocturnal enuresis: A placebo controlled trial of two antidepressant drugs. Archives of Diseases in Childhood 1996;75:62-66.
106. Thomsen W, Reid WB, Hebeler J. Effect of Tofranil on enuretic boys. Diseases of the Nervous System 1967;28(3):167-169.
107. Danquah SA. Comparative treatment of nocturnal enuresis among Ghanaian school children. Psychopathologie Africaine 1975;11(3):363-373.
108. Wright L, Craig SC. A comparative study of amphetamine, ephedrine-atropine mixture, placebo and behavioral conditioning in the treatment of nocturnal enuresis. Journal - Oklahoma State Medical Association 1974;67(10):430-433.
109. Gjessing J. Investigation and therapy of nocturnal enuresis in the Fredrica Medical District [Danish]. Ugeskift for Laeger 1968;130(48):2053-2056.
110. Liederman PC, Wasserman DH, Liederman VR. Desipramine in the treatment of enuresis. Journal of Urology 1969;101(3):314-316.
111. Lovering JS, Tallett SE, McKendry JB. Oxybutynin efficacy in the treatment of primary enuresis. Pediatrics 1988;82(1):104-6.
112. Harrington M. Phenmetrazine in the treatment of nocturnal enuresis. The Practitioner 1960;185:343-346.
113. Butler RJ, Forsythe WI, Robertson J. The body-worn alarm in the treatment of childhood enuresis. British Journal of Clinical Practice 1990;44(6):237-41.
114. Bollard J, Nettelbeck T. A comparison of dry bed training and standard urine alarm conditioning treatment of childhood bed wetting. Behaviour Research and Therapy 1981;19(3):215-226.
115. Fielding D. The response of day and night wetting children and children who wet only at night to retention control training and the enuresis alarm. Behaviour Research and Therapy 1980;18(4):305-317.
116. Geffken G, Johnson SB, Walker D. Behavioral interventions for childhood nocturnal enuresis: the differential effect of bladder capacity on treatment progress and outcome. Health Psychology 1986;5(3):261-72.
117. Jehu D, Morgan RT, Turner RK, Jones A. A controlled trial of the treatment of nocturnal enuresis in residential homes for children. Behaviour Research and Therapy 1977;15(1):1-16.
118. Scholander T. [Treating enuresis nocturna by a combination of medicines and conditioning]. Lakartidningen 1968;65(46):4552-6.
119. Sloop E, Kennedy W. Institutionalised retarded nocturnal enuretics treated by a conditioning technique. American Journal of Mental Deficiency 1973;77:717-721.
120. Taylor PD, Turner RK. A clinical trial of continuous, intermittent and over learning "bell and pad" treatments for nocturnal enuresis. Behaviour Research and Therapy 1975;13(4):281-293.
121. Wagner WG, Matthews R. The treatment of nocturnal enuresis: a controlled comparison of two models of urine alarm. Journal of Developmental & Behavioral Pediatrics 1985;6(1):22-6.

122. Bollard J. A 2 year follow-up of bed wetters treated by dry bed-training and standard conditioning. Behaviour Research and Therapy 1982;20(6):571-580.
123. Bollard J, Nettelbeck T. A component analysis of dry-bed training for treatment for bed wetting. Behaviour Research and Therapy 1982;20(4):383-390.
124. Bollard J, Nettelbeck T, Roxbee L. Dry bed training for childhood bed wetting: A comparison of group with individually administered parent instruction. Behaviour Research and Therapy 1982;20(3):209-217.
125. Keating JC, Butz RA, Burke E, Heimberg RG. Dry bed training without a urine alarm: Lack of effect of setting and therapist contact with child. Journal of Behaviour Therapy and Experimental Psychiatry 1983;14(2):109-115.
126. Harris LS, Purohit AP. Bladder training and enuresis: A controlled trial. Behaviour Research and Therapy 1977;15(6):485-490.
127. Leboeuf C, Brown P, Herman A, Leembruggen K, Walton D, Crisp T. Chiropractic care of children with nocturnal enuresis: a prospective outcome study. Journal of Manipulative & Physiological Therapeutics 1991;14(2):110-5.
128. Edwards SD, van der Spuy HJ. Hypnotherapy as a treatment for enuresis. Journal of Child Psychology & Psychiatry & Allied Disciplines 1985;26(1):161-70.
129. Wagner W, Johnson SB, Walker D, Carter R, Wittner J. A controlled comparison of two treatments for nocturnal enuresis. Journal of Pediatrics 1982;101(2):302-7.
130. Azrin NH, Foxx RM. A rapid method of toilet training the institutionalised retarded. Journal of Applied Behaviour Analysis 1971;4:89-99.
131. Bradbury MG, Meadow SR. Combined treatment with enuresis alarm and desmopressin for nocturnal enuresis. Acta Paediatrica 1995; 84:1014-1018.
132. de Jonge GA. Human Chorionic Gonadotrophin ("Pregnyl") in the treatment of Nocturnal enuresis. Developmental Medicine and Child Neurology 1973;15:497-499.
133. De Leon G, Mandell W. A comparison of conditioning and psychotherapy in the treatment of functional enuresis. Journal of Clinical Psychology 1966;22:326-330.
134. Doleys DM, Ciminero AR, Tollinson JW, Williams CL, Wells KC. Dry-bed training and retention control training: A comparison. Behaviour Therapy 1977;8(4):541-548.
135. Esperanca M, Gerrard JW. Nocturnal enuresis: comparison of the effect of imipramine and dietary restriction on bladder capacity. Canadian Medical Association Journal 1969;101:65-68.
136. Evans JH, Meadow SR. Desmopressin for bed wetting: length of treatment, vasopressin secretion, and response. Archives of Disease in Childhood 1992;67(2):184-8.
137. Ferrie BG, MacFarlane J, Glen ES. DDAVP in young enuretic patients: a double-blind trial. British Journal of Urology 1984;56(4):376-8.
138. Fisher GW, Murray F, Walley MR, Kiloh LG. A controlled trial of imipramine in the treatment of nocturnal enuresis in mentally subnormal patients. American Journal of Mental Deficiency 1963;67:536 - 538.
139. Fordham KE, Meadow SR. Controlled trial of standard pad and bell alarm against mini alarm for nocturnal enuresis. Archives of Disease in Childhood 1989;64(5):651-6.
140. Jensen PO, Jensen PH. Treatment of nocturnal enuresis with emepronium bromide (Cetiprin). A controlled clinical trial [Danish]. 1982;144(30):2224-2226.
141. Laybourne PCJ, Roach NE, Ebbesson B, Edwards S. Double-blind study of the use of imipramine (Tofranil) in enuresis. Psychosomatics 1968;9(5):282-285.
142. Mariuz MJ, Walters CJ. Enuresis in non-psychotic boys treated with imipramine. American Journal of Psychiatry 1963;120:597-599.
143. Metin A, Aykoi N. Diclofenac sodium suppository in the treatment of primary nocturnal enuresis. International Urology and Nephrology 1992;24(2):113-117.

144. Nentwich HJ. Therapy of enuresis with a pediatric tablet of propiverin (Mictonettes) [German]. Kinderarzlichte Praxis 1986;54(6):329-333.
145. Otto-Unger G. Treatment of the unstable bladder in children with the anticholinergic agent propiverin hydrochloride (mictonorm/mictonets) [German]. Zeitschrift Fur Urologie Und Nephrologie 1985;78(3):145-152.
146. Rapoport JL, Mikkelsen EJ, Zavadil A, et al. Childhood enuresis. II. Psychopathology, tricyclic concentration in plasma, and antienuretic effect. Archives of General Psychiatry 1980;37(10):1146-52.
147. Ronen T, Wozner Y, Rahav G. Cognitive intervention in enuresis. Child and Family Behaviour Therapy 1992;14(2):1-14.
148. Schjetne OB, Uri O. Nocturnal enuresis. Treatment with an antidepressive (Tofranil) controlled by a placebo in a double-blind trial on 28 children [Norwegian]. Tidsskrift for Den Norske Laegeforening 1970;90(9):873-876.
149. Stenberg A, Lackgren G. Desmopressin tablets in the treatment of severe nocturnal enuresis in adolescents. Pediatrics 1994;94(6 Pt 1):841-6.
150. Agarwala S, Heycock JB. A controlled trial of imipramine (Tofranil) in the treatment of childhood enuresis. British Journal of Clinical Practice 1968;22(7):296-298.
151. al-Waili NS. Indomethacin suppository to treat primary nocturnal enuresis: double blind study. Journal of Urology 1989;142(5):1290-1292.
152. Baker BL. Symptom treatment and symptom substitution in enuresis. Journal of Abnormal Psychology 1969;74:42-49.
153. Banerjee S, Srivastav A, Palan B. Hypnosis and self-hypnosis in the management of nocturnal enuresis: a comparative study with imipramine therapy [see comments]. American Journal of Clinical Hypnosis 1993;36(2):113-9.
154. Batislam E, Nuhoglu B, Peskircloglu L, et al. A prostaglandin synthesis inhibitor, Diclofenac sodium, in the treatment of primary nocturnal enuresis. Acta Urologica Belgica 1995;63(3):35-38.
155. Breger E. Hydroxyzine hydrochloride and methylphenidate hydrochloride in the management of enuresis. Journal of Pediatrics 1962;61:443-447.
156. Breger E. Meprobamate in the management of enuresis. Journal of Pediatrics 1961;59:571-576.
157. Cupalova R, Tabarka K, Adamova J, Vachutkova M. Our experience with faradization of urinary bladder in enuretic children. Acta Univ Palacki Olomuc Fac Med 1988;119:459-464.
158. Dubow E. Enuresis: adjunctive therapy. Clinical investigations with an ephedrine-atropine mixture. Clinical Pediatrics 1966;5(3):177-180.
159. Elinder G, Soback S. Effect of Uristop on primary nocturnal enuresis. A prospective randomized double-blind study. Acta Paediatrica Scandinavica 1985;74(4):574-8.
160. Finley WW, Wansley RA. Auditory intensity as a variable in the conditioning treatment of enuresis nocturna. Behaviour Research and Therapy 1977;15(2):181-185.
161. Forsythe WI, Merrett JD, Redmond A. Enuresis and Psychoactive drugs. British Journal of Clinical Practice 1972;26(3):116-118.
162. Forsythe WI, Merrett JD, Redmond A. A controlled clinical trial of trimipramine and placebo in treatment of enuresis. British Journal of Clinical Practice 1972;26(3):19-121.
163. Friday GA, Feldman EC. Treatment of enuretic children with imipramine (Tofranil). Clinical Pediatrics 1966;5(3):175-176.
164. Hojsgaard A, Genster H. Effect of Uristop in children with enuresis. A prospective randomised clinical trial [Danish]. Ugeskrift for Laeger 1979;141(10):647-648.

165. Holt KS. Drug treatment of enuresis: controlled trials with propantheline, amphetamine and pituitary snuff. Lancet 1956;ii:1334-1336.
166. Iester A, Marchesi A, Cohen A, Iester M, Bagnasco F, Bonelli R. Functional enuresis: pharmacological versus behavioral treatment. Childs Nervous System 1991;7(2):106-8.
167. Kennedy WA, Sloop EW. Methedrine as an adjunct to conditioning treatment for nocturnal enuresis in normal and institutionalised retarded subjects. Psychological Reports 1968;22:997-1000.
168. Khorana AB. A controlled trial of imipramine hydrochloride on enuresis. Curr. Med Pract 1972;Ind16(7):305-308.
169. Khosroshahi HE, Bozkurt V, Sadikoglu N, Atakan C. Treatment of nocturnal enuresis: a placebo-controlled trial with piracetam, diphenylhydantoin and psychotherapy. Turkish Journal of Pediatrics 1989;-31(3):215-20.
170. Kline AH. Diazepam and the management of nocturnal enuresis. Clin Med 1968;75:20-22.
171. Marconi AM, Bocciardi A, Roggia A, Fava C. Oxybutynin chloride in enuresis (randomised clinical study). Urologia 1984;51:262-263.
172. McKendry JB, Stewart DA, Khanna F, Netley C. Primary enuresis: relative success of three methods of treatment. Canadian Medical Association Journal 1975;113(10):953-5.
173. Mehrotra SN, L. L, Srivastava JR, Singh SB. Evaluation of various methods in treatment of enuresis. Indian Pediatrics 1980;17:519-522.
174. Netley C, Khanna F, McKendry JB, Lovering JS. Effects of different methods of treatment of primary enuresis on psychologic functioning in children. Canadian Medical Association Journal 1984;131(6):577-579.
175. Poussaint AF, Ditman KS, Greenfield R. Amitriptyline in childhood enuresis. Clinical Pharmacology and Therapeutics 1966;7(1):21-25.
176. Wallace IR, Forsythe WI. The treatment of enuresis: a controlled clinical trial of propantheline, propantheline-and-phenobarbitone and a placebo. British Journal of Clinical Practice 1969;23(5):207-210.
177. Yurdakok M, Kinik E, Beduk Y, Guvenc H, Us O. Treatment of enuresis: a study with imipramine, amitriptyline, chlordiazepoxide-clidinium and piracetam. Turkish Journal of Pediatrics 1986;28(3):171-175.
178. Yurdakok M, Kinik E, Guvenc H, Beduk Y. Viloxazine versus imipramine in the treatment of enuresis. Turkish Journal of Pediatrics 1987;29(4):227-230.
179. Bennett GA, Walkden VJ, Curtis RH, et al. Pad and Buzzer training, dry-bed training and stop-start training in the treatment of primary nocturnal enuresis. Behavioural Psychotherapy 1985;13(4):309-319.
180. Caceres J. Enuresis: Cortical control or social reinforcement? Behaviour Therapist 1982;5(2):65-67.
181. Drew LR. Control of enuresis by imipramine. Medical Journal of Australia 1966;2(26):1225-1227.
182. General Practitioner Research Group. General practitioner clinical trials: Sedative and stimulant compared in enuresis. Practitioner 1970;204(222):584-586.
183. Hanson RH, Thompson T, Wieseler NA. Methodological considerations in enuresis-treatment research: A three treatment comparison. Behavior Modification 1988;12(3):335-352.
184. Harrison JS, Albino VJ. An investigation into the effects of imipramine hydrochloride on the incidence of enuresis in institutionalised children. South African Medical Journal 1970;44(9):253-255.

185. Houts AC, Peterson JK, Whelan JP. Prevention of relapse in full-spectrum home training for primary enuresis: A components analysis. Behaviour Therapy 1986;17(4):462-469.
186. Houts AC, Whelan JP, Peterson JK. Filmed versus live delivery of full-spectrum home training for primary enuresis: Presenting the information is not enough. Journal of Consulting and Clinical Psychology 1987;55(6):902-906.
187. Leys D. Value of propantheline bromide in treatment of enuresis. British Medical Journal 1956;1:549-550.
188. Lynch NT, Grunert BK, Vasudevan SV, Severson RA. Enuresis: comparison of two treatments. Archives of Physical Medicine and Rehabilitation 1984;65(2):98-100.
189. Milner G, Hills NF. A double-blind assessment of anti-depressants in the treatment of 212 enuretic patients. Medical Journal of Australia 1968;1(22):943-947.
190. Moffatt ME, Kato C, Pless IB. Improvements in self-concept after treatment of nocturnal enuresis: randomized controlled trial. Journal of Pediatrics 1987;110(4):647-52.
191. Treffert DA. An evaluation of imipramine in enuresis. Am J. Psychiat 1964;121:178-179.
192. Valentine AA, Maxwell C. Enuresis in severely subnormal children: a clinical trial of imipramine. Journal of Mental Subnormality 1968;12(2)).
193. Azrin NH, Sneed TJ, Fox RM. Dry-bed training - rapid elimination of childhood enuresis. Behaviour Research and Therapy 1974;12:147-156.
194. Azrin NH, Thienes PM. Rapid elimination of enuresis by intensive learning without a conditioning apparatus. Behavior Therapy 1978;9(3):342-354.
195. Dorison EE, Blackman S. Imipramine in the treatment of adult enuretics. Am J. Psychiat 1962;119:474.
196. Fava GA, Cracco L, Facco L. Positive reinforcement and enuresis. Italian Journal of Psychology 1981;8(2):149-152.
197. Forrester RM, Stein Z, Susser MW. A trial of conditioning therapy in nocturnal enuresis. Developmental Medicine and Child Neurology 1964;6:158-166.
198. Hicks WR, Barnes EH. A double-blind study of the effect of imipramine on enuresis in 100 naval recruits. American Journal of Psychiatry 1964;120:812-814.
199. Kooijman MJ, Bosch JD. Supportive research on treatment of enuresis with a urine alarm [Dutch]. Nederlands Tijdschrift voor Psychology en haar Grensgebieden 1986;41(7):325-326.
200. Lindholm O. A clinical study of esucos in a mentally retarded clientele. Acta Neurologica et Psychiatrica Belgica 1967;67 Suppl:49-64.
201. McConaghy N. A controlled trial of imipramine, amphetamine, pad and bell conditioning and random awakening in the treatment of nocturnal enuresis. Medical Journal of Australia 1969;2(5):237-239.
202. Salmon MA. The concept of day-time treatment for primary nocturnal enuresis. In: Kolvin I, MacKeith RC, Meadow SR, eds. Bladder control and enuresis. London: William Heinemann Medical Books, 1973:189-194.
203. Whelan JP, Houts AC. Effects of waking schedule on primary enuretic children treated with full-spectrum home training. Health Psychology 1990;9(2):164-176.
204. Moffatt MEK, Cheung M. Predicting treatment outcome with conditioning alarms. Scandinavian Journal of Urology and Nephrology 1995;Suppl 173:119-121.
205. Rushton HG, Belman AB, Skoog S, Zaontz MR, Sihelnik S. Predictors of response to desmopressin in children and adolescents with monosymptomatic nocturnal enuresis. Scandinavian Journal of Urology and Nephrology 1995;Suppl 173:109-111.
206. Morison M. Family perspectives on bed wetting in young people. Aldershot: Avebury, 1996.

207. Pedersen PS, Hejl M, Kjoller SS. Desamino-D-arginine vasopressin in childhood nocturnal enuresis. Journal of Urology 1985;133(1):65-6.
208. Klauber GT. Clinical efficacy and safety of desmopressin in the treatment of nocturnal enuresis [review]. Journal of Pediatrics 1989;114(Pt 2):719-722.
209. Wille S. Primary nocturnal enuresis in children. Background and treatment. Scandinavian Journal of Urology & Nephrology. Supplementum 1994;156::1-48.
210. Abrams AE. Imipramine in enuresis. Am. J. Psychiat 1963;120:177 -.
211. Adler HM. Enuresis in recruits: double blind study with equanil and review of the literature. USAF Med. J. 1959;10:767-786.
212. Al Waili NS. Diclofenac sodium in the treatment of primary nocturnal enuresis: double-blind cross over study. 13 1986;2:139-142.
213. Alderton HR. Imipramine in childhood nocturnal enuresis: relationship of time of administration to effect. Canadian Psychiatric Association Journal 1967;12(2):197-203.
214. Alderton HR. Imipramine in childhood enuresis: further studies on the relationship of time of administration to effect. Canadian Medical Association Journal 1970;102(11):1179-1180.
215. Alison M, Didier J. Treatment of children with amitriptyline-perphenazine combination. French Revue de Neuropsychiatrie Infantile et D'Hygiene Mentale de L'Enfance 1973;21(7):475-480.
216. Arai M, Arima M, Uchimura N, et al. [Therapeutics for enuresis nocturna - with special reference to comparison between imipramine and placebo on the basis of double-blind test]. Igaku No Ayumi 1971;Progress in Medicine(77):8.
217. Arajarvi T, Kivalo A, Nyberg P. Effect of antidepressants on enuretic school children. Psychiatria Fennica 1977;1977:83-87.
218. Arroe M, Barner Rasmussen P. Treatment of nocturnal enuresis by means of an alarm system worn by the patient. Ugeskr. Laeg. 1979;141(11):729-731.
219. Azrin NH, Thienes-Hontos P, Besalel-Azrin V. Elimination of enuresis without conditioning apparatus: An extension by office instruction of the child and parents. Behaviour Therapy 1979;10(1):14-19.
220. Baller W, Schalock H. Conditioned response treatment of enuresis. Exceptional Children 1956;22:233-247.
221. Baller WJ, Giangreco CJ. Correction of nocturnal enuresis in deaf children. Volta Rev. 1970;72:545-549.
222. Bergman JS. Effectiveness of college students in an incentive community program for chronic hospitalised children. Community Mental Health Journal 1976;12(2):192-202.
223. Berhle FC, Elkin MT, Laybourne PC. Evaluation of a conditioning device in the treatment of nocturnal enuresis. Pediatrics 1956;17:849-855.
224. Bernasconi S, Monti G. Minerva Pediatr 1992;34:131-134.
225. Besalel VA, Azrin NH, P. T-H, McMorrow. An evaluation of a parents' manual for training enuretic children. Behaviour Research and Therapy 1980;18:358-360.
226. Bhatia MS, Dhar NK, Rai S, Malik SC. Enuresis: an analysis of 82 cases. Indian Journal of Medical Sciences 1990;44(12):337-342.
227. Boggs SR, Geffken GR, Johnson SB, Silverstein J. Behavioral treatment of nocturnal enuresis in children with insulin-dependent diabetes mellitus. Journal of Pediatric Psychology 1992;17(1):111-8.
228. Bollard RJ, Woodroffe P. The effect of parent administered dry bed training on nocturnal enuresis in children. Behaviour Research and Therapy 1977;15:159-165.

229. Bouchard MA, Joly J, Cardinal JF. Diurnal urinary retention in the treatment of enuresis: Comparison of univariate and multi variate analysis. Canadian Journal of Behavioural Science 1981;13(1):53-64.
230. Butler RJ, Holland P. The investigation of a structured programme of withdrawal of medication in the prevention of relapse following treatment for childhood nocturnal enuresis: A pilot study. Unpublished manuscript.
231. Buttarazzi PJ. Oxybutynin Chloride. Ditropan) in enuresis 1977;Journal of Urology(118).
232. Cai ZM. Relation between the extent of distinctness of propagated sensation along channels and therapeutic effect of acupuncture on enuresis in Senegal patients. Chen Tzu Yen Chiu 1987;12(Suppl 2):65 -66.
233. Ceresoli A, Zanetti G, Seveso M, et al. Treatment of adult primary uncomplicated nocturnal enuresis by pelvic floor training and behaviour modification therapy. Archivio Italiano Di Urologia, Andrologia 1993;65(5):561-2.
234. Cigna RM, Chiaramonte C, Lo Gaglio C, Milazzo M, Lo Piparo M, De Grazia E. [Enuresis in children. Diagnostic assessment and treatment]. [Italian]. Minerva Pediatrica 1989;41(7):371-3.
235. Collins RW. Importance of bladder cue contingency in the conditioning treatment for enuresis. Journal of Abnormal Psychology 1973;82:299-308.
236. Cortina J. Enuresis and its homoeopathic treatment: study of twenty cases treated with ilex paraguensis. British Homoeopathy Journal 1994;83(4):220-222.
237. Creer T, Davis, M.H. Using a staggered wakening procedure with enuretic children in an institutional setting. J. Behav. Ther. Exp. Psychiatr 1975;6:23-25.
238. Crisp AH, Sireling LI, Faizey J. Nocturnal activity and the enuresis alarm device. Postgraduate Medical Journal 1984;60(702):280-281.
239. Danielsson B, Forsberg P, Svensson M. Behandling av sangvatning i primarvarden. Lakartidningen 1985;82:2579-.
240. Davidson JR, Douglass E. Nocturnal enuresis: a special approach to treatment. British Medical Journal 1950;I:1345-1347.
241. De Castro R, Casolari E, Ricci S. Use of Oxybutynin chloride (Ditropan) in treatment of enuresis. Riv. Ital. Ped. 1985;11:208-211.
242. de Jonge GA. Treatment of nocturnal enuresis with imipramine. Tofranil).[Dutch] 1972;Nederlands Tijdschrift voor Geneeskunde(116):32.
243. Devlin JB, O'Cathain C. Predicting treatment outcome in nocturnal enuresis. Archives of Disease in Childhood 1990;65(10):1158-61.
244. D'Hollander L, Vaneck L. Treatment of enuresis by imipramine and amitriptyline in retarded children [French]. Acta Neurologica and Psychiatrica Belgica 1967;67(5):359-375.
245. Dimson SB. DDAVP and urine osmolality in refractory enuresis. Archives of Disease in Childhood 1986;61(11):1104-7.
246. Dische S. Management of enuresis. British Medical Journal 1971;2:33-36.
247. Doeschate IOM, van Gool JD, Messer AP. Long-term results of dry-bed training in 153 adolescents with nocturnal enuresis. Unpublished manuscript. 1994:
248. Eckford SD, Swami KS, Jackson SR, Abrams PH. Desmopressin in the treatment of nocturia and enuresis in patients with multiple sclerosis. British Journal of Urology 1994;74:733-735.
249. Edelstein BAea. Effects of caffeine withdrawal on nocturnal enuresis, insomnia and behaviour restraints. Journal of Consulting and Clinical Psychology 1984;52(5):857-862.
250. Egger J, Carter CH, Soothill J, Wilson J. Effect of diet treatment on enuresis in children with migraine or hyperkinetic behaviour. Clinical Pediatrics 1992;31(5):302-307.

251. el-Sadir A, Sabry AA, Addel-Rahman M, el-Barnachawy R, Koritim M. Treatment of primary nocturnal enuresis by oral androgen mesterolone. A clinical and cystometric study. Urology 1990;36(4):331-335.
252. Elmer M, Norgaard JP, Djurhuus JC, Adolfsson T. Terodiline in the treatment of diurnal enuresis in children. Scandinavian Journal of Primary Health Care 1988;6(2):119-124.
253. Elmer M, Adolfsson T, Norgaard JP, Djurhuus JC. [Diurnal enuresis in childhood is effectively treated with Terodiline]. Lakartidningen 1991;88(10):850-851.
254. Elzinga-Plomp A, Boemers TML, Messer AP, Vijverberg MAW, De-Jong TPV, Van Gool JD. Treatment of enuresis risoria in children by self-administered electric and imaginary shock. British Journal of Urology 1995;76(6):775-778.
255. Figueroa TE, Benaim E, Griggs ST, Hvizdala EV. Enuresis in sickle cell disease. Journal of Urology : 1995;153(6):1987-9.
256. Finley WW, Besserman RL, Bennett LF, Clapp RK, Finley PM. The effect of continuous, intermittent, and "placebo" reinforcement on the effectiveness of the conditioning treatment for enuresis nocturna. Behaviour Research & Therapy 1973;11(3).
257. Finley WW, Wansley RA. Use of intermittent reinforcement in a clinical-research program for the treatment of enuresis nocturna. J. Pediatr. Psychiatr 1976;1:24-27.
258. Finley WW, Rainwater AJ, Johnson G. Effect of varying alarm schedules on acquisition and relapse parameters in the conditioning treatment of enuresis. Behaviour Research and Therapy 1982;20:69-80.
259. Fly-Hansen A, Jorgensen TM. Treatment of nocturnal enuresis with the pad and bell system. Scandinavian Journal of Urology and Nephrology 1995;Suppl 173:101-102.
260. Forsythe WI, Merrett JD. A controlled trial of imipramine (Tofranil) and nortriptyline (Allegron) in the treatment of enuresis. British Journal of Clinical Practice 1969;23(5):210-215.
261. Forsythe WI, Redmond A. Enuresis and the electric alarm: study of 200 cases. British Medical Journal 1970;1:211-213.
262. Freyman R. Follow-up study of enuresis treated with a bell apparatus. J. Child Psychl. Psychiatr 1963;4:199-206.
263. Fritz GK, Rockney RM, Yeung AS. Plasma levels and efficacy of imipramine treatment for enuresis. Journal of the American Academy of Child & Adolescent Psychiatry 1994;33(1):60-4.
264. General Practitioner Research Group. Imipramine in enuresis. Practitioner 1969;202(213):94-97.
265. Geppert TV. Management of nocturnal enuresis by conditioned response. Journal of the American Medical Association 1953;152:381-383.
266. Gillison TH, Skinner JL. Treatment of nocturnal enuresis by the electric alarm. British Medical Journal 1958;ii:1268-1272.
267. Goel KM, Thomson RB, Gibb EM, McAinsh TF. Evaluation of nine different types of enuresis alarm. Archives of Disease in Childhood 1984;59:748-755.
268. Grassetti F, Di Noia D, Paone F, Alcini E. Enuresis: pathogenic and therapeutic study with Oxybutynin chloride. Ped Oggi 1986;1:47-51.
269. Griffiths P, Meldrum C, McWilliam R. Dry bed training in the treatment of nocturnal enuresis in childhood. Journal of Child Psychology and Psychiatry and Allied Disciplines 1982;23(4):485-495.
270. Hagglund TB, Parkkulainen KV. Enuretic Children treated with imipramine (Tofranil): A cystometric study. Annales Paediatriae Fenniae 1964;11:53-59.

271. Halliday S, Meadow SR, Berg I. Successful management of daytime enuresis using alarm procedures: a randomly controlled trial. Archives of Disease in Childhood 1987;62(2):132-7.
272. Hjalmas K. SWEET: the Swedish enuresis trial. Scandinavian Journal of Urology and Nephrology 1995;Suppl 173:89-93.
273. Hofler G. Out-patient treatment with amitriptyline of diurnal and nocturnal enuresis. Wien Med Wochenschr 1978;128(21):683-685.
274. Hunt S, Adams M. Bibliotherapy-based Dry-Bed Training: a pilot study. Behavioural Psychotherapy 1989;17(3):290-301.
275. Ishigooka M, Hashimoto T, Sasagawa I, Izumiya K, Nakada T. Terodiline in the treatment of nocturnal enuresis in children. International Urology and Nephrology 1992;24(5):509-513.
276. Jarvis GJ. Bladder Drill for the treatment of enuresis in adults. British Journal of Urology 1982;54:118-119.
277. Jones KS, Tibbetts MA. Pituitary snuff, propantheline and placebos in the treatment of enuresis. Journal of Medical Science 1959;105:371-381.
278. Jorgensen OS, Lober M, Christiansen J, Gram L. Plasma concentration and clinical effect in imipramine treatment of childhood enuresis. Clinical Pharmacokinetics 1980;5(4):386-93.
279. Kahane M. An experimental investigation of a conditioning treatment and a preliminary study of the psychoanalytic theory of the etiology of nocturnal enuresis. American Psychologist 1955;10:369.
280. Kales A, Kales JD, Jacobson A, Humphrey FJn, Soldatos CR. Effect of imipramine on enuretic frequency and sleep stages. Pediatrics 1977;60(4):431-436.
281. Kamel M, Mooro H. Treatment of nocturnal enuresis with preludin. Journal of the Egyptian Medical Association 1969;52(4):329-332.
282. Kaplan SL, Brei tM, Gauthier B, Busner J. A comparison of three nocturnal enuresis treatment methods. J. Am. Acad Child and Adolescent Psychiatr. 1989;28:282-286.
283. Kapoor VK, Saksena PN. Methyl amphetamine hydrochloride (methedrine) in enuresis. Indian Journal of Pediatrics 1969;36(256):169-170.
284. Kardash S, Hillman ES, Werry J. Efficacy of imipramine in childhood enuresis: a double-blind control study with placebo. Canadian Medical Association Journal 1968;99(6):263-266.
285. Key DW, Bloom DA, Sanvordenker J. Low dose DDAVP in nocturnal enuresis. Clinical Pediatrics 1992;31:299-301.
286. Kondo A, Gotoh M, Kato K, Saito M, Sasakibara T, Yamada H. Treatment of persistent enuresis. Results of severing a tight filum terminale. British Journal of Urology 1988;62:42-45.
287. Korczyn AD, Kish I. The mechanism of imipramine in enuresis nocturna. Clinical & Experimental Pharmacology & Physiology 1979;6(1):31-5.
288. Kurokawa K, Ohtaguro K. Treatment of nocturnal enuresis with tryptanol (amitriptyline hydrochloride). Chiryo Journal of Therapy 1963;45:72-.
289. Kyneb P, Biorn Henriksen T. Behandling af enuresis hos skoleborn. Manedsskr Prakt Laegegern 1975;53(V):250-259.
290. Lake B. Controlled trial of nortriptyline in childhood enuresis. Medical Journal of Australia 1968;2(14):582-585.
291. Lake CR, Mikkelsen EJ, Rapoport JL, Zavadil AP, Kopin IJ. Effect of imipramine on norepinephrine and blood pressure in enuretic boys. Clinical Pharmacology and Therapeutics 1979;25(6):647-653.

292. Li M, Li X. [Observation on therapeutic effectiveness of moxibustion with moxa thread]. [Chinese]. Chen Tzu Yen Chiu Acupuncture Research 1992;17(4):288-9.
293. Libert MH. The use of Viloxazine in the treatment of primary enuresis. Current Therapeutic Research 1991;49(3):335-339.
294. Lines DR. A double blind trial of amitriptyline in enuretic children. Medical Journal of Australia 1968;2(7):307-308.
295. Lovibond SH. Intermittent reinforcement in behavior therapy. Behaviour Research and Therapy 1963;1:127-132.
296. Lovibond SH. Conditioning and Enuresis: New York, Macmillan. Oxford: Pergamon, 1964.
297. Luiselli JK. Secondary diurnal enuresis: evaluation of cuing and reinforcement interventions with a sensory-impaired youth. Journal of Mental Deficiency Research 1987;31:287-292.
298. Manglick MP, Buchanan N. Imipramine in primary nocturnal enuresis and the value of blood level measurements [letter]. Medical Journal of Australia 1992;156(1):68-9.
299. Marshall S, Marshall HH, Lyon RP. Enuresis: an analysis of various therapeutic approaches. Pediatrics 1973;52:813-817.
300. Matthiesen TB, Rittig S, Djurhuus JC, Norgaard JP. A dose titration, and an open 6-week efficacy and safety study of desmopressin tablets in the management of nocturnal enuresis. Journal of Urology 1994;151(2):460-3.
301. Mayon-White RM. A controlled trial of propantheline in bed wetting. British Medical Journal 1956;I:550-.
302. Meadow R, Berg I. Controlled trial of imipramine in diurnal enuresis. Archives of Disease in Childhood 1982;57(9):714-6.
303. Meijer A. Value of imipramine for bed wetting children. Diseases of the Nervous System 1965;26:309-311.
304. Miller PR, Champelli JW, Dinello FA. Imipramine in the treatment of enuretic school children. A double-blind study. American Journal of Diseases of Children 1968;115(1):17-20.
305. Miller K, Goldberg S, Atkin B. Nocturnal enuresis: experience with long term use of intranasally administered desmopressin. In: Meadow SR, ed. Desmopressin in enuresis. Proceedings of an International Symposium held at the Royal College of Physicians. London: Horus Medical Publications, 1988:56-62.
306. Miller K, Goldberg S, Atkin B. Nocturnal enuresis: experience with long-term use of intra nasally administered desmopressin. Journal of Pediatrics 1989;114:723-726.
307. Mishra PC, Agarwal VK, Rahman H. Therapeutic trial of amitriptyline in the treatment of nocturnal enuresis - a controlled study. Indian Pediatrics 1980;17(3):279-285.
308. Monda JM, Husmann DA. Primary nocturnal enuresis: a comparison among observation, imipramine, desmopressin acetate and bed-wetting alarm systems. Journal of Urology : 1995;154(2 Pt 2):745-8.
309. Motta RW. Factors related to the efficacy of treatment of enuresis. Psychological Reports 1979;44(3 Pt 2):1183-1188.
310. Noack CH. Enuresis nocturna - a long term study of 44 children treated with imipramine hydrochloride (Tofranil) and other drugs. Medical Journal of Australia 1964;1:191-194.
311. Olness K. The use of self hypnosis in the treatment of nocturnal enuresis. Clinical Pediatrics 1975;14:273-275 & 278-279.
312. Paschalis AP, Kimmel HD, Kimmel D. Further study of diurnal instrumental conditioning in the treatment of enuresis nocturna. Journal of Behaviour Therapy and Experimental Psychiatry 1972;3:253-256.

313. Persson-Junemann C, Seemann O, Kohrmann KU, Junemann KP, Alken P. Comparison of urodynamic findings and response to Oxybutynin in nocturnal enuresis. Eur. Urol 1993;24:92-96.
314. Petersen KE, Andersen OO. Treatment for nocturnal enuresis with imipramine and related preparations: A double blind study with placebo. Acta Paediactrica Scandinavica 1971;60(2):244.
315. Petersen KE, Andersen OO, Hansen T. Mode of action and relative value of imipramine and similar drugs in the treatment of nocturnal enuresis. European Journal of Clinical Pharmacology 1974;7(3):187-94.
316. Peterson RA, Wright RL, Hanlon CC. The effect of extending the CS-UCS interval on the effectiveness of the conditioning treatment of enuresis. Behaviour Research and Therapy 1969;7(4):351-357.
317. Philpott MG, Flasher M. The treatment of enuresis: further clinical experience with imipramine. British Journal of Clinical Practice 1970;24(8):327-329.
318. Polak L, Skoricova M, Dimova N, Havlickova H, Okruhlica L, Molcan J. Treatment of enuresis with sydnocarb. Activas Nervosa Superior 1981;23(4):263-264.
319. Porot M, Girard J. [The use of amitriptyline in syrup form in the treatment of enuresis in children]. French Ann Med Psychol 1970;128(1):781-787.
320. Poussaint AF, Ditman KS. A clinical trial of protriptyline in childhood enuresis. Psychosomatics 1965;6(6):413-416.
321. Protinsky H, Dillard C. Enuresis: a family therapy model. Psychotherapy: Theory, Research and Practice 1983;20:81-89.
322. Ramsden PD, Hindmarsh JR, Price DA, Yeates WK, Bowditch JD. DDAVP for adult enuresis - a preliminary report. British Journal of Urology 1982;54(3):256-258.
323. Ritvo ER, Ornitz EM, Gottlieb, et al. Arousal and non-arousal enuretic events. American Journal of Psychiatry 1969;126(1):77-84.
324. Rodriguez E, Delucchi MA, Cano F, Wolff E. Desmopressin acetate treatment for nocturnal enuresis. Revista Chilena de Pediatria 1995;66(3):136-139.
325. Sacks S, De Leon G. Conditioning two types of enuretics. Behaviour Research and Therapy 1973;11(4):653-654.
326. Sacks S, De Leon G. Conditioning functional enuresis: Follow-up after retraining. Behaviour Research and Therapy 1983;21(6):693-694.
327. Sacks S, De Leon G, Blackman S. Psychological changes associated with conditioning functional enuresis. Journal of Clinical Psychology 1973;29:271-276.
328. Schulz D, Sureth H, Lubisch G. Comparison of two behaviour modifications methods for treatment of bed wetting. Zeitschrift fur Klinische Psychologie 1978;7(2):141-148.
329. Shah LP. Amitriptyline in the treatment of enuresis. Indian Pediatrics 1971;8(11):767-769.
330. Simeon J, Maguire L, Lawrence S. Maprotiline effects in children with enuresis and behavioural disorders. Prog. Neuro Psychopharmacol 1981;5(5-6):495-498.
331. Singh SB, Nigram A, Liu L, Mehrotra SN, Srivastava JRl. Medical, psychological and combined therapy in the cases of enuresis: A comparative study. Indian Journal of Clinical Psychology 1980;7(2):99-102.
332. Site J, Gaillard L, Delphin D, Messy P, Feisthauer J. [966 cases of enuresis - clinical study and trial of imipramine, antispasmodic and sedative therapy]. Lyon Med 1974;231(7):623-631.
333. Smith EH, Gonzalez R. Nortriptyline hydrochloride in the treatment of enuresis in mentally retarded boys. American Journal of Mental Deficiency 1967;71:825-.

334. Smith L. Training severely and profoundly mentally handicapped nocturnal enuretics. Behaviour, Research and Therapy 1981;19:67-74.
335. Soulayrol R, Julien D. Note on the comparative effect of 2 drugs recommended for enuresis [French]. Revue de Neuropsychiarie Infantile et D'Hygiene mentale de L'Enfance 1970;18(12):933-942.
336. Steffens J, Netzer M, Isenberg E, Alloussi S, Ziegler M. Vasopressin deficiency in primary nocturnal enuresis. Results of a controlled prospective study. European Urology 1993;24(3):366-70.
337. Steinicke O. Imipramine therapy of enuresis - material from Julemaerkehjemmene [Danish]. Nordisk Medicin 1971;85(3):89.
338. Stenberg A, Lackgren G. Treatment with oral desmopressin in adolescents with primary nocturnal enuresis. Efficacy and long-term effect. Clinical Pediatrics 1993;Spec No::25-7.
339. Stenberg A, Lackgren G. Desmopressin tablet treatment in nocturnal enuresis. Scandinavian Journal of Urology and Nephrology 1995;Suppl 173:95-99.
340. Taylor IO. A scheme for the treatment of enuresis by electric buzzer apparatus. Medical Officer 1963;110:139-340.
341. Tiptaft RC, Woodhouse CRJ, Badenoch DF. Mazindol for nocturnal enuresis. British Journal of Urology 1984;56:641-643.
342. Tosto A, Dattolo E, Brigandini R, Pironti M, Di Cello V, Rizzo M. Early antibiotic therapy following urodynamic examination. Results of a randomised controlled study [Italian]. Minerva Urologica e Nefrologica 1989;41(4):271-273.
343. Tret'iakova EE. [The effectiveness of the combined treatment of enuresis]. [RUSSIAN]. Zhurnal Nevropatologii I Psikhiatrii Imeni S - S - Korsakova 1990;90(5):121-4.
344. Turner RK, Taylor P. Conditioning treatment of nocturnal enuresis in adults: preliminary results. Behaviour, Research and Therapy 1974;12:41-52.
345. Turner RK, Young GC. CNS stimulant drugs and conditioning treatment of nocturnal enuresis: a long term follow-up study. Behaviour Research and Therapy 1966;4:225-228.
346. Turner RK, Young GC, Rachman S. Treatment of nocturnal enuresis by conditioning techniques. Behaviour Research and Therapy 1970;8:367-381.
347. Ulf O. Comparative study of Preparyl, Tofranil and Tryptizol in enuresis nocturna of children with severe developmental disturbances. Svenska Lakartidningen 1964;61:3894.
348. van Londen A, van Londen-Barentsen MW, van Son MJ, Mulder GA. Arousal training for children suffering from nocturnal enuresis: a 2 year follow-up. Behaviour Research & Therapy 1993;31(6):613-5.
349. van Londen A, van Londen-Barentsen MW, van Son MJ, Mulder GA. Relapse rate and subsequent parental reaction after successful treatment of children suffering from nocturnal enuresis: a 2 year follow-up of bibliotherapy. Behaviour Research & Therapy 1995;33(3):309-11.
350. Van Londen MJ, Van Londen-Barentsen WM. Arousal training for nocturnal enuresis in children: A waking device as prompt for desirable behaviour [Dutch]. Gedragstherapie 1991;24(4):223-233.
351. van Son M, van Heesch N, Mulder G, van Londen A. The effectiveness of dry bed training for nocturnal enuresis in adults: a 3, 5, 6 years follow-up. Behaviour Research & Therapy 1995;33(5):557-9.
352. van Son MJ, Mulder G, van Londen A. The effectiveness of Dry Bed Training for nocturnal enuresis in adults. Behaviour Research & Therapy 1990;28(4):347-9.

353. Wagner WG, Johnson JT. Childhood nocturnal enuresis: the prediction of premature withdrawal form behavioural conditioning. Journal of Abnormal Child Psychology 1988;16(6):687-692.
354. Waitzel ID, Gallagher EJ, Marshall RJ. Control of enuresis in disturbed adolescent boys. Journal of the National Medical Association 1969;61(6):474-475.
355. Werry JS, Aman MG, Dowrick P, Lampen EL. Imipramine and chlordiazepoxide in enuresis (proceedings). Psychopharmacology Bulletin 1977;13(2):38-39.
356. Werry JS, Cohrssen J. Enuresis: An etiologic and therapeutic study. The Journal of Pediatrics 1965;6:43-431.
357. Werry JS, Dowrick PW, L LE, Vamos MJ. Imipramine in enuresis - psychological and physiological effects. Journal of Child Psychology and Child Psychiatry and Allied Disciplines 1975;16(4):298-299.
358. Wickes IG. Treatment of persistent enuresis with the electric buzzer. Archives of Disease in Childhood 1958;33:160-164.
359. Wilken-Jensen K. Nocturnal bed wetting: an attempt to treat school children with banthine and probanthine. Acta Paediatrica (Uppsala) 1959;48:78 - 84.
360. Williams CL, Doleys DM, Ciminero AR. A two year follow-up of enuretic children treated with dry-bed training. Journal of Behaviour Therapy and Experimental Psychiatry 1978;9(3):285-286.
361. Wood CM, Butler RJ, Penney MD, Holland PC. Pulsatile release of arginine vasopressin (AVP) and it's effect on response to desmopressin in enuresis. Scandinavian Journal of Urology & Nephrology. Supplementum : 1994;163:93-101.
362. Woodhead DM, Hall TC, Snodgrass WT. An effective control of benign enuresis. Journal of Urology 1967;97(1):98-100.
363. Yamanishi T, Igarashi T, Murakami S, et al. [A comparative study of the effects of drug therapy and bladder training therapy]. [Japanese]. Hinyokika Kiyo - Acta Urologica Japonica 1988;34(1):102-6.
364. Young GC, Morgan RT. Conditioning treatment of enuresis: Auditory intensity. Behaviour Research and Therapy 1973;11(4):411-416.
365. Young GC. A "staggered-wakening" procedure in the treatment of enuresis. The Medical Officer 1964;111:142-143.
366. Young GC. Conditioning treatment of enuresis. Developmental Medicine and Child Neurology 1965;7:557-562.
367. Young GC, Morgan RTT. Over learning in the conditioning treatment of enuresis: a long term follow-up study. Behaviour Research and Therapy 1972;10:419-420.
368. Young GC, Morgan RTT. Over learning in the conditioning treatment of enuresis. Behaviour Research and Therapy 1972;10:147-151.
369. Young GC, Turner RK. CNS stimulant drugs and conditioning treatment of nocturnal enuresis. Behaviour Research and Therapy 1965;3:93-101.
370. Marconi AM, Felici E, Roggia A, Torelli F. Anticholinergic treatment in the therapy of primary enuresis: Effectiveness of Oxybutynin chloride in a controlled study of 58 patients [Italian]. Pediatrica Medica e Chirurgica 1985;7(4):573-576.
371. NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness. CRD Report 4. NHS CRD, University of York.
372. Der Sinonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-188.