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Deshpande AV, Caldwell PHY, Sureshkumar P.
Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics).
Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD002238.
DOI: [10.1002/14651858.CD002238.pub2](https://doi.org/10.1002/14651858.CD002238.pub2).

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[Intervention Review]

Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics)

Aniruddh V Deshpande¹, Patrina HY Caldwell², Premala Sureshkumar³

¹Department of Surgery and Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. ²Discipline of Paediatrics and Child Health, The Children's Hospital at Westmead Clinical School, University of Sydney, Westmead, Australia. ³Centre for Kidney Research, Royal Alexandra Hospital for Children, Parramatta, Australia

Contact address: Patrina HY Caldwell, Discipline of Paediatrics and Child Health, The Children's Hospital at Westmead Clinical School, University of Sydney, Locked Bag 4001, Westmead, NSW, Australia. Patrinac@chw.edu.au.

Editorial group: Cochrane Incontinence Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 12, 2012.

Citation: Deshpande AV, Caldwell PHY, Sureshkumar P. Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics). *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD002238. DOI: [10.1002/14651858.CD002238.pub2](https://doi.org/10.1002/14651858.CD002238.pub2).

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ABSTRACT

Background

Enuresis (bedwetting) is a socially stigmatising and stressful condition which affects around 15% to 20% of five-year olds and up to 2% of young adults. Although there is a high rate of spontaneous remission, the social, emotional and psychological costs to the children can be great. Drugs (including desmopressin, tricyclics and other drugs) have often been tried to treat nocturnal enuresis.

Objectives

To assess the effects of drugs other than desmopressin and tricyclics on nocturnal enuresis in children and to compare them with other interventions.

Search methods

We searched the Cochrane Incontinence Group Specialised Register of trials (searched 15 December 2011), which includes searches of MEDLINE and CENTRAL, to identify published and unpublished randomised and quasi-randomised trials. The reference lists of relevant articles were also searched.

Selection criteria

All randomised trials of drugs (excluding desmopressin or tricyclics) for treating nocturnal enuresis in children up to the age of 16 years were included in the review. Trials were eligible for inclusion if children were randomised to receive drugs compared with placebo, other drugs or behavioral interventions for nocturnal enuresis. Studies which included children with daytime urinary incontinence or children with organic conditions were also included in this review if the focus of the study was on nocturnal enuresis. Trials focused solely on daytime wetting and trials of adults with nocturnal enuresis were excluded.

Data collection and analysis

Two review authors independently assessed the quality of the eligible trials and extracted data. Differences between review authors were settled by discussion with a third review author.

Main results

A total of 40 randomised or quasi-randomised controlled trials (10 new in this update) met the inclusion criteria, with a total of 1780 out of 2440 children who enrolled receiving an active drug other than desmopressin or a tricyclic. In all, 31 different drugs or classes of drugs

were tested. The trials were generally small or of poor methodological quality. There was an overall paucity of data regarding outcomes after treatment was withdrawn.

For drugs versus placebo, when compared to placebo indomethacin (risk ratio [RR] 0.36, 95% CI 0.16 to 0.79), diazepam (RR 0.22, 95% CI 0.11 to 0.46), mestorelone (RR 0.32, 95% CI 0.17 to 0.62) and atomoxetine (RR 0.81, 95% CI 0.70 to 0.94) appeared to reduce the number of children failing to have 14 consecutive dry nights. Although indomethacin and diclofenac were better than placebo during treatment, they were not as effective as desmopressin and there was a higher chance of adverse effects. None of the medications were effective in reducing relapse rates, although this was only reported in five placebo controlled trials.

For drugs versus drugs, combination therapy with imipramine and oxybutynin was more effective than imipramine monotherapy (RR 0.68, 95% CI 0.50 to 0.94) and also had significantly lower relapse rates than imipramine monotherapy (RR 0.35, 95% CI 0.16 to 0.77). There was an overall paucity of data regarding outcomes after treatment was withdrawn.

For drugs versus behavioural therapy, bedwetting alarms were found to be better than amphetamine (RR 2.2, 95% CI 1.12 to 4.29), oxybutynin (RR 3.25, 95% CI 1.77 to 5.98), and oxybutynin plus holding exercises (RR 3.3, 95% CI 1.84 to 6.18) in reducing the number of children failing to achieve 14 consecutive dry nights.

Adverse effects of drugs were seen in 19 trials while 17 trials did not adequately report the occurrence of side effects.

Authors' conclusions

There was not enough evidence to judge whether or not the included drugs cured bedwetting when used alone. There was limited evidence to suggest that desmopressin, imipramine and enuresis alarms therapy were better than the included drugs to which they were compared. In other reviews, desmopressin, tricyclics and alarm interventions have been shown to be effective during treatment. There was also evidence to suggest that combination therapy with anticholinergic therapy increased the efficacy of other established therapies such as imipramine, desmopressin and enuresis alarms by reducing the relapse rates, by about 20%, although it was not possible to identify the characteristics of children who would benefit from combination therapy. Future studies should evaluate the role of combination therapy against established treatments in rigorous and adequately powered trials.

PLAIN LANGUAGE SUMMARY

Drug treatment for children with bedwetting (nocturnal enuresis) but not including the drug types desmopressin or tricyclics

Bedwetting (nocturnal enuresis) is the involuntary loss of urine at night without an underlying organic disease as the cause. It can result in social problems, sibling teasing and lowered self esteem. It affects around 15% to 20% of five-year olds, and up to 2% of adults. Many different types of drugs have been used to treat children with bed wetting. There is not enough reliable evidence to show that drugs other than desmopressin or tricyclics reduce bedwetting in children during treatment when used in isolation, despite their risk of unwanted side effects. In other Cochrane reviews, alarms triggered by wetting, desmopressin and tricyclic drugs have been shown to work during treatment. However, alarms have a more sustained effect than desmopressin and tricyclics after treatment has finished. The adverse effects of alarm therapy (tiredness and waking other members of the family) are relatively benign and self limiting compared with the adverse effects of drugs. One class of drugs (anticholinergic drugs) appears to improve the efficacy of other established treatments such as tricyclics, bedwetting alarms and desmopressin. The cost of treating children with bedwetting with alarm therapy or drugs may vary in different countries.

BACKGROUND

This is one of seven reviews of interventions for bedwetting, or nocturnal enuresis. The others focus on desmopressin (Glazener 2004a), tricyclics and related drugs (Glazener 2004b), enuresis alarm therapy (Glazener 2005a), simple behavioural therapy (Glazener 2004b), complex behavioural and educational interventions (Glazener 2004a) and complementary and miscellaneous therapy (Huang 2011). This review is an update of previous updates by Glazener et al (Glazener 2000; Glazener 2003) based on the original review by Lister-Sharp and her colleagues at the NHS Centre for Reviews and Dissemination at the University of York, UK (Lister-Sharp 1997).

With the promotion by the International Children's Continence Society (ICCS) of using standardised nomenclature in paediatric continence research (Neveus 2006) and the improved understanding about the pathophysiology of nocturnal enuresis, there has been an emphasis on classifying enuresis as either monosymptomatic or non-monosymptomatic. As a result, there have been more published studies examining the effects of anticholinergic medication both as monotherapy and as an adjunct to other therapies. The ICCS has also defined initial and long term treatment success. Unfortunately, the older studies have usually not used these definitions (or were unclear about their definition of initial success). There were no studies that included two-year follow up and therefore long term success could not be assessed.

Prevalences and causes

Nocturnal enuresis is common in children. Estimating the prevalence of nocturnal enuresis is difficult because there is variation in the diagnostic criteria, with very few studies using ICCS definitions (de Jonge 1973; Krantz 1994; Neveus 2006). The generally quoted prevalence rates are 15% to 20% of five-year olds, 7% of seven-year olds, 5% of 10-year olds, 2% to 3% of teenagers and 0.5% to 2% of adults, with a spontaneous remission rate of 14% until adolescence (Blackwell 1989; Forsythe 1974; Rutter 1973). The prevalence of nocturnal enuresis is higher amongst children in residential care (Morgan 1970).

Butler proposed the conceptual model that nocturnal enuresis occurs when there is poor arousal from sleep in response to a full bladder sensation with overactivity of bladder functioning or excessive overnight urine production, or both (Butler 2004). There are also many known risk factors for nocturnal enuresis including:

- genetic influences (APA 1980; Bakwin 1971; Bakwin 1973; Eiberg 1995),
- delay in attaining bladder control (Jarvelin 1989; Koff 1995),
- physiological factors (Djurhuus 1992; Norgaard 1993) such as constipation, faecal incontinence, daytime urinary incontinence, caffeine consumption (Blackwell 1989; Sureshkumar 2009),
- sleep apnoea and upper airway obstructive symptoms (Maizels 1993),
- and psychological factors (Devlin 1991; Moffatt 1989; Rutter 1973; Shaffer 1977).

It is thought that these risk factors impact on sleep arousal, bladder stability and overnight urine production.

Description of the condition

Nocturnal enuresis is the intermittent involuntary loss of urine at night, in the absence of physical disease, at an age when a child could reasonably be expected to be dry (by consensus, at a developmental age of five years) (APA 1980; Neveus 2006; WHO 1992). Nocturnal enuresis has a significant negative impact on the child's psychosocial wellbeing (Hagglof 1998). Children with nocturnal enuresis who do not have daytime bladder symptoms are deemed to have 'monosymptomatic nocturnal enuresis' (Neveus 2006). Between 10% and 28% of children who wet the bed also have bladder problems during the day (Forsythe 1974), and are said to have 'non-monosymptomatic nocturnal enuresis' (Neveus 2006). Although daytime urinary incontinence is a significant problem it is usually considered separately to nocturnal enuresis as the aetiologies underlying the two conditions are thought to be different (Jarvelin 1989). Physical causes such as structural abnormalities and functional disorders of the urinary tract, including overactive bladder syndrome or urinary tract infections, are more often found in children who also have daytime wetting (Jarvelin 1990). If daytime symptoms are present, investigations to identify physical (organic) causes such as urinary tract dysfunction, congenital malformation and neurogenic disorders are usually necessary (Djurhuus 1992), with treatment initially focused on addressing the daytime urinary symptoms (Hjalmas 2004).

The understanding of the pathogenic mechanisms in nocturnal enuresis continues to evolve. We now know that between 10% and 28% of children who wet the bed also have bladder problems during the day (Forsythe 1974), and are said to have non-monosymptomatic nocturnal enuresis (Neveus 2006), with a total of 6.6% of children having combined daytime urinary incontinence and nocturnal enuresis (Sureshkumar 2009). However, daytime urinary incontinence will be reviewed in a separate Cochrane review.

Description of the intervention

Pharmacological, psychological or behavioural and a variety of 'unconventional' interventions are commonly used for treating bedwetting.

Pharmacological interventions include desmopressin, tricyclic drugs (amitriptyline, dothiepin, doxepin, trimipramine, clomipramine, desipramine, imipramine, lofepramine, nortriptyline and protriptyline), drugs related to the tricyclics (viloxazine, desipramine, mianserin and maprotiline), amphetamine, diazepam and oxybutynin; although some are now contraindicated.

Behavioural interventions include alarms, overlearning, star charts, reward systems, retention control training, fluid deprivation, lifting, scheduled waking, complex behavioural interventions (for example dry bed training and full spectrum home training).

Other therapies include psychotherapy, surgery and complementary therapies. These are all discussed in separate reviews.

The current review is restricted to pharmacological treatment with drugs (other than desmopressin or tricyclic and related antidepressants) or to other interventions only if they are compared with such drugs. None of these drugs are now in current use for children with enuresis as primary therapy. Certain

drugs may have increased clinical applicability in the future, as supplementary medications which improve bladder function.

Drugs other than desmopressin or tricyclics included in this review

Non-steroidal anti-inflammatory drugs (NSAIDs)

Indomethacin and diclofenac have been tested in trials to treat enuresis. They are believed to act by prostaglandin or cyclooxygenase inhibition pathways. The rationale for this treatment is based on the findings that reduced levels of prostaglandins (PGE2) correlate to a favourable response to treatment ([Sener 1998](#)).

Psychoactive drugs

Historically, amphetamine (stimulant) and diazepam (tranquillizer) were used for treating nocturnal enuresis, in order to alter sleep levels. Other psychoactive drugs used in the treatment of enuresis include meprobamate (anxiolytic) and hydroxyzine (antihistamine); ephedrine sulphate (adrenergic); amphetamine and methedrine (stimulants); chlordiazepoxide (long-acting benzodiazepine, anxiolytic and anticholinergic); piracetam (GABA analogue, said to increase the activity of the associative brain system); emepronium (antimuscarinic or atropine-like action); methscopolamine (hyoscine metantrate: antimuscarinic or atropine-like action); chlorprothixene (antipsychotic and sedative, blocks post-synaptic dopamine receptors and alpha receptors) and phenmetrazine (sympathomimetic used for anorexia). The rationale for the use of these medications in enuresis was guided by an earlier belief that nocturnal enuresis was the result of a conflict or anxiety. Many of these drugs are now considered to be contraindicated for treating nocturnal enuresis in children. Some drugs are not licensed or have had their licences discontinued, including emepronium (Cetepin) and methscopolamine.

Anticholinergics

More recently, oxybutynin (antispasmodic, anticholinergic) has been tried primarily for treating detrusor overactivity, which would be expected to result in improvement in daytime as well as night-time wetting. This is possibly because a subgroup of children with nocturnal enuresis (non-monosymptomatic nocturnal enuresis) also have associated detrusor overactivity or nocturnal detrusor overactivity.

Other drugs

Drugs used to treat attention deficit hyperactivity disorder such as methylphenidate and atomoxetine (selective norepinephrine reuptake inhibitor) have also been tested.

The following interventions will be included only if they are compared with any of the above drugs.

Other interventions

Desmopressin

The most commonly used drug for treating nocturnal enuresis is desmopressin (a vasopressin analogue). When administered at bedtime, it helps to reduce nocturnal urine production with a beneficial effect on the symptom of enuresis in a large proportion (70%) of children with nocturnal enuresis. There is a separate desmopressin for nocturnal enuresis review ([Glazener 2002](#)).

Tricyclic drugs

Tricyclic drugs act on the central nervous system by blocking the synaptic alpha receptor reuptake of noradrenaline and serotonin into the neurons, thus prolonging their effects. The usual clinical use of tricyclics is as antidepressants. Additionally, they have anticholinergic or antispasmodic effects, local anaesthetic properties and affect the sleep centre in the brain. Tricyclic drugs include imipramine, amitriptyline, dothiepin, doxepin, trimipramine, clomipramine, lofepramine, nortriptyline and protriptyline. Drugs which are pharmacologically related are viloxazine, desipramine and mianserin. The beneficial effect of imipramine was initially attributed to its anticholinergic effects, but it has been recently shown that imipramine can be of help in children who have not responded to anticholinergic therapy ([Gepertz 2004](#)), suggesting that there may be another mechanism of action. There is a separate review on tricyclics for nocturnal enuresis ([Glazener 2003a](#)).

Behavioural and other interventions

Behavioural interventions include enuresis alarm therapy and overlearning ([Glazener 2005a](#)); complex behavioural interventions such as dry bed training, multi-dimensional behavioural training ([Glazener 2004a](#)); and simple behavioural interventions such as retention control training, fluid deprivation, lifting, random wakening and star charts ([Glazener 2004b](#)). Other interventions include complementary and miscellaneous interventions such as acupuncture, hypnosis, chiropractic and homeopathy ([Huang 2011](#)). These are evaluated in separate reviews.

The current review is restricted to pharmacological treatment with drugs (other than desmopressin or tricyclic and related antidepressants) or to other interventions only if they are compared with such drugs. None of these drugs are now in current use for treating children with enuresis as primary therapy. Certain drugs may have increased clinical applicability in the future as supplementary medications which may be shown to improve bladder function.

With improved understanding, newer treatment strategies are being developed often in combination with the established therapies. These strategies commonly incorporate drugs which modulate urinary bladder function, with an ever widening spectrum of drugs from different pharmacological classes being tested for the treatment of nocturnal enuresis as monotherapy or combination therapy.

Why it is important to do this review

Nocturnal enuresis is common in children. It has a significant negative impact on the child's psychosocial wellbeing ([Hagglof 1998](#)). Currently, bedwetting alarms and desmopressin therapy are the established treatment for nocturnal enuresis, albeit with a subgroup of patients who do not respond. Although drug therapies other than desmopressin or tricyclics have been tried for nocturnal enuresis, little is known of their impact.

This review summarises the findings of the trials of all such medications (drugs other than desmopressin or tricyclics) used for the treatment of nocturnal enuresis. This review and its subsequent updates will play an important role in streamlining therapy, particularly of the children with refractory nocturnal enuresis. The findings of this review will also lay foundations for further research

into the application of drugs to maximise the treatment outcomes in all types of children with nocturnal enuresis.

OBJECTIVES

To determine the effects of drugs (other than desmopressin or tricyclics) on the treatment of children with nocturnal enuresis.

The following comparisons were made:

1. drugs versus no treatment or placebo;
2. one drug versus another;
3. drugs, or placebo drug treatments, versus behavioural interventions;
4. a higher dose of a drug versus a lower dose.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised studies of drugs (other than desmopressin or tricyclics) versus any comparable treatments for nocturnal enuresis.

Types of participants

Children (as defined by the trialists, usually up to age 16 years) with nocturnal enuresis.

Types of interventions

Any trial which used drugs (other than desmopressin or tricyclics) in at least one arm of the study.

Comparison interventions included desmopressin, tricyclic or related drugs and other interventions (for example alarm treatment, random waking and star charts).

Types of outcome measures

Primary outcomes

- Mean number of wet nights per week during treatment
- Number of children not attaining 14 consecutive dry nights during treatment

Secondary outcomes

- Mean number of wet nights per week when children were followed up after treatment stopped
- Number of children failing or relapsing after treatment stopped (during follow up)
- Adverse effects

Search methods for identification of studies

We did not impose any language or other restrictions on any of the searches.

Electronic searches

This review has drawn on the search strategy developed for the Incontinence Review Group. Relevant trials were identified from the Cochrane Incontinence Group Specialised Register of controlled trials. The register is described along with the group search strategy under the Incontinence Group's [module](#) in *The Cochrane Library*. The register contains trials identified from the Cochrane Central

Register of Controlled Trials (CENTRAL), MEDLINE, CINAHL and handsearching of journals and conference proceedings. The date of the most recent search of the register for this review was 15 December 2011.

The Incontinence Group Specialised Register was searched using the Group's keyword system. The terms used to search are given below:

```
(TOPIC.URINE.ENURESIS*)
AND
({DESIGN.CCT*} OR {DESIGN.RCT*})
AND
({INTVENT.CHEM.DRUG*})
```

Key: * = truncation symbol.

(All searches were of the keyword field of Reference Manager 12, Thomson Reuters.)

Searching other resources

The reference list of a previous systematic review of enuresis treatments was also searched ([Lister-Sharp 1997](#)).

Data collection and analysis

The studies for this review were assessed using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Selection of studies

The titles and, where possible, abstracts of all studies located by the searches were checked by at least two review authors to identify those likely to be evaluations of the effects of interventions for nocturnal enuresis. Full papers were then obtained and assessed to identify studies that met the inclusion criteria.

Data extraction and management

The data were extracted using a standard form. Included trial data were processed as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Where appropriate, the results were converted to the mean and standard deviation of the number of wet nights per week, or the number of children failing to achieve full response during treatment, defined as 14 consecutive dry nights at the end of the treatment period, or the mean number of wet nights per week at follow up after stopping treatment, or the number who did not achieve full response during treatment plus those who relapsed after stopping active treatment (at follow up after completion of treatment). Where a mean value was reported with no standard deviation, we entered the data into 'Other data' tables.

Assessment of risk of bias in included studies

Standard risk of bias items according to the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) were assessed for each study. These include:

- adequate sequence generation;
- allocation concealment;
- blinding of study participants;
- blinding of study personnel;
- blinding of outcome assessors;
- incomplete outcome data addressed;

- freedom from selective reporting;
- free of other bias (e.g. whether children with daytime wetting or had physical (organic) causes of their enuresis were specifically excluded, or whether there were baseline differences between groups, or whether there was a washout period in crossover trials).

Measures of treatment effect

We intended, where possible, to calculate standardised effect sizes and 95% confidence intervals: weighted mean differences (WMD) where outcomes were continuous variables and risk ratios (RR) where they were dichotomous. The WMD would be weighted by the inverse of the variance, and given as difference in number of wet nights per week. Negative values indicate fewer wet nights. A fixed-effect model was used for calculation of 95% confidence intervals (CI).

Unit of analysis issues

The unit of allocation was individual patients. Crossover trials have been indicated by a suffix # after the trial ID. Crossover trials were only included if the design was deemed to be appropriate for the question being investigated. Otherwise, data from the first arm of crossover trials was used as for parallel group data.

Dealing with missing data

When intention-to-treat analysis was not mentioned in the paper, or if some participants were not analysed in the group to which they were randomised, we looked for sufficient information to restore them to the correct group. If participants could not be analysed in their allocated groups, this was mentioned in the review ('Risk of bias' table and in the 'Risk of bias' section of the text).

Where there were missing outcome data in the included studies, the primary analysis used the number of participants with available data as the denominator (that is 'available case' analysis). We also attempted to contact the authors. Standard deviations were obtained from standard errors, CI, t values or P values that related to the differences between means in two groups, according to the *Cochrane Handbook for Systematic Reviews of Interventions* Section 7.7.3.3

Assessment of heterogeneity

Differences between trials were further investigated if statistically significant heterogeneity was found at the 10% significance level

using the χ^2 test or assessment of the I^2 statistic to quantify the degree of heterogeneity (Higgins 2011), or appeared obvious from visual inspection of the results. A fixed-effect model was used if there was little or no heterogeneity and a random-effects model used when there was statistically significant heterogeneity.

Assessment of reporting biases

We planned to investigate the possibility of publication bias and related biases if any meta-analyses were performed that involved 10 or more studies, but this did not occur.

Data synthesis

Meta-analysis was performed according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) if there was a sufficient number of trials for each comparison. A fixed-effect model was used in the analysis. If there was substantial heterogeneity, assuming treatment effects differed between trials, we planned to use the random-effects method to produce an overall summary estimate.

Subgroup analysis and investigation of heterogeneity

If there was heterogeneity, we planned to investigate it using subgroup analysis restricted to primary outcomes and sensitivity analysis.

Sensitivity analysis

If necessary, data were analysed using both random-effects and fixed-effect models. Where appropriate, the possible effects of missing data were explored in a sensitivity analysis (for example, assuming the 'worst' and 'best' case scenarios for all participants with missing outcome data).

RESULTS

Description of studies

Results of the search

The literature search produced a total of 429 abstracts and titles to assess. The flow of literature through this assessment process is shown in the PRISMA flowchart in (Figure 1).

Figure 1. PRISMA study flow diagram.

Figure 1. (Continued)

11 studies
were included
in the
quantitative
synthesis

The current review is the fourth minor update of this review (Glazener 2000). Ten extra trials (Alawwa 2010#; Austin 2008; el-Sadr 1990a; Esmaeili 2008; Gelotte 2009; Korczyn 1979#; Lee 2005; Neveus 2008#; Van Hoeck 2008; Yuksek 2003) have been included, and two studies excluded (Lovering 1988#; Yurdakok 1986).

Included studies

The various searches located 103 potentially eligible primary studies (115 reports) investigating drugs (other than desmopressin or tricyclics) for the treatment of enuresis (Figure 1). Thus, 40 randomised controlled trials (47 reports) were included. They included 2440 children of whom 1780 received an active drug other than desmopressin or a tricyclic. Only eight trials had more than 100 participants and the median number of participants for the included studies was 58. Of these trials, 25 were added in the last substantive update of this review (Glazener 2003), and a further 10 in this one.

Drugs (other than desmopressin and tricyclics) were compared with treatments that are recognised to be effective in 10 trials: desmopressin (Natochin 2000; Sener 1998); tricyclics (Ingle 1968; Kunin 1970#; Moltke 1979; Petersen 1974#; Tahmaz 2000); and alarms (Forrester 1964; Kennedy 1968; Wright 1974). Follow-up data were available from only eight trials (Dubow 1966; el-Sadr 1990a; Esmaeili 2008; Forsythe 1972; Ingle 1968; Leys 1956; Tahmaz 2000; Van Hoeck 2008). Follow up was not possible in crossover trials (as children had been exposed to both treatments by the end of the trial) and was often not available in the remainder of trials because children who were still wet or who relapsed were then given other treatment.

Interventions and comparisons

The active drugs included were as follows.

Anticholinergics

- Atropine plus ephedrine (Dubow 1966; Wright 1974)
- Tolterodine (Austin 2008; Neveus 2008#)
- Scopolamine butylbromide (Korczyn 1979#)
- Oxybutynin (Lee 2005; Marconi 1985; Tahmaz 2000; Van Hoeck 2008; Varan 1996; Yuksek 2003)

NSAIDs

- Diclofenac (Al-Waili 1986#; Batislam 1995; Natochin 2000)
- Indomethacin, suppository (Al-Waili 1989#; Sener 1998), oral (Varan 1996)
- Ibuprofen and pseudoephedrine (Gelotte 2009)

Psychoactive drugs (including stimulants and hypnotics)

- Hydroxyzine (Breger 1962)
- Amphetamine (Forrester 1964; Wright 1974)

- Chlordiazepoxide plus amitriptyline (Forsythe 1972)
- Chlorprothixene (Gjessing 1968#)
- Triclofos (GP Research Gp 1970#)
- Meprobamate (Breger 1961)
- Meprobamate plus hydroxyzine (Ingle 1968)
- Phenmetrazine (Harrington 1960#)
- Emepronium (Cetepirin, Petersen 1974#)
- Piracetam (Khosroshahi 1989)
- Diazepam (Kline 1968)
- Oxazepam (Serenid) (Salmon 1973#)
- Chlordiazepoxide (Librium) (Salmon 1973#)
- Indoramin (Shaffer 1978#)
- Phenobarbitone (Wallace 1969)
- Atomoxetine (Sumner 2006)

Others

- Hydrochlorthiazide (Alawwa 2010#)
- Methylphenidate (Breger 1962)
- Ephedrine or pseudoephedrine (GP Research Gp 1970#; Kunin 1970#; Varan 1996)
- Methedrine (Kennedy 1968)
- Propantheline (Leys 1956)
- Dicyclomine (Marconi 1985)
- Furosemide (Lasix) (Moltke 1979)
- Propantheline (Mayon-White 1956; Wallace 1969)

These totalled 31 different types or classes of drugs. None of these drugs are in current clinical practice as primary therapy for bedwetting in children.

Comparison interventions included:

- placebo (Alawwa 2010#; Al-Waili 1986#; Al-Waili 1989#; Austin 2008; Batislam 1995; Breger 1961; Breger 1962; Dubow 1966; el-Sadr 1990a; Forsythe 1972; Gelotte 2009; Gjessing 1968#; Harrington 1960#; Khosroshahi 1989; Kline 1968; Korczyn 1979#; Leys 1956; Mayon-White 1956; Moltke 1979; Natochin 2000; Neveus 2008#; Petersen 1974#; Salmon 1973#; Sener 1998; Shaffer 1978#; Sumner 2006; Tahmaz 2000; Van Hoeck 2008; Wallace 1969; Wright 1974);
- imipramine (Batislam 1995; Ingle 1968; Kunin 1970#; Moltke 1979; Petersen 1974#; Tahmaz 2000);
- alarms triggered by wetting (Forrester 1964; Kennedy 1968; Wright 1974);
- play and supportive therapy (Khosroshahi 1989);
- desmopressin (Natochin 2000; Sener 1998).

Excluded studies

After scrutiny of the titles and abstracts:

- 30 studies were excluded because they were not randomised trials;
- four studies were excluded because they tested acupuncture therapy (not drugs) (Cheng 2008; Jiang 2000; Xiao 1997; Zou 2008);
- one study tested desmopressin (Marson 1955);
- 12 were excluded because they focused on children with daytime wetting or who had organic causes such as detrusor overactivity alone (Al-Waili 2000; Ayan 2007; Caione 1995; Elmer 1988#; Festqe 1989; Hellstrom 1989; Misselwitz 1999; Naglo 1979; Szabo 1999; Szabo 2002; Thompson 1976; Thorup 1982);
- three studies were excluded because children were moved between trial arms or other protocol violations resulted in unreliable data (Holt 1956; McConaghy 1969; Mikkelsen 1980);
- three studies were excluded because the participants did not meet the inclusion criteria (Ayan 2007; Kroll 2006; Lopez 2003);
- one study was excluded because the drug arm (oxybutynin) was not a component of the randomised part of the trial (Rodriguez 2001);

- seven others were excluded because although the studies included children with enuresis, the focus of the study was not on treating enuresis and outcomes were not related to the improvement or otherwise in number of wet nights (Chertin 2007; Jensen 1982#; Lake 1979; Lovering 1988#; Martins 1994; Saeedalzakerin 2000; Yurdakok 1986);
- one study awaits classification (Cupalova-Naglova 1970, Czech language).

Risk of bias in included studies

Allocation

Random sequence generation

Of the 40 included trials (Figure 2; Figure 3), only three used adequate sequence generation (Forrester 1964; Gelotte 2009; Salmon 1973#). Nine used quasi-randomisation methods (for example alternation, date of birth or case record number) (Austin 2008; Esmaeili 2008; Ingle 1968; Kennedy 1968; Leys 1956; Mayon-White 1956; Natochin 2000; Van Hoeck 2008; Yuksek 2003) and in 28 studies there were insufficient information to determine the adequacy of the sequence generation process.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias) - participants	Blinding (performance bias) - care givers	Blinding (detection bias) - outcome assessor	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Alawwa 2010#	?	?	?	?	?	+	-	+
Al-Waili 1986#	?	?	?	?	?	?	?	?
Al-Waili 1989#	?	?	?	?	?	?	?	?
Austin 2008	-	?	+	+	?	+	-	+
Batistam 1995	?	?	?	?	?	?	?	-
Breger 1961	?	?	+	+	?	-	?	+
Breger 1962	?	?	?	+	?	-	?	+
Dubow 1966	?	?	+	?	?	+	?	+
el-Sadr 1990a	?	?	+	?	?	+	+	-
Esmaeili 2008	-	?	?	?	?	-	-	-
Forrester 1964	+	?	?	?	-	?	-	+
Forsythe 1972	?	?	?	?	?	?	?	+
Gelotte 2009	+	+	+	+	+	+	-	+
Gjessing 1968#	?	?	?	?	?	+	?	?
GP Research Gp 1970#	?	?	?	?	?	+	+	?
Harrington 1960#	?	?	+	+	?	-	?	+
Ingle 1968	-	?	?	?	?	+	+	+
Kennedy 1968	-	?	?	?	?	+	-	-
Khosroshahi 1989	?	?	-	-	-	-	+	?
Kline 1968	?	?	+	-	?	+	+	+
Korczyn 1979#	?	?	?	?	?	-	-	-
Kunin 1970#	?	+	?	?	?	?	?	?

Figure 3. (Continued)

Kunin 1970#	?	+	?	?	?	?	?	?
Lee 2005	?	?	?	?	?	-	-	-
Leys 1956	-	?	+	+	+	+	+	-
Marconi 1985	?	?	?	?	?	-	-	+
Mayon-White 1956	-	+	+	?	?	+	+	?
Moltke 1979	?	?	?	?	?	+	+	+
Natochin 2000	-	?	-	-	-	+	+	+
Neveus 2008#	?	?	?	?	?	+	-	+
Petersen 1974#	?	?	?	?	?	?	?	?
Salmon 1973#	+	?	?	?	?	?	?	?
Sener 1998	?	?	-	-	?	?	?	?
Shaffer 1978#	?	?	?	+	?	+	-	-
Sumner 2006	?	?	?	?	?	+	+	+
Tahmaz 2000	?	?	?	?	?	?	?	-
Van Hoeck 2008	?	-	-	-	?	+	+	?
Varan 1996	?	?	?	?	?	+	?	+
Wallace 1969	?	?	+	?	?	+	-	+
Wright 1974	?	?	-	-	-	+	+	?
Yukse 2003	?	?	-	-	?	+	?	?

Allocation concealment

Overall, allocation concealment methods were poorly reported in the published trials. 36 trials did not give enough information to determine the adequacy of the allocation concealment process (Figure 2; Figure 3). The allocation concealment was adequate only in three trials.

Blinding

Participants, their parents, the healthcare professional looking after the child and the investigator conducting the data analysis are potential sources of bias. In assessing performance bias, blinding of the participants, their parents and the healthcare professionals is important. Blinding of participants and parents is usually clearly reported in the majority of trials comparing one drug with another or comparing a drug with placebo. However, in trials of drugs versus behavioural therapy blinding of participants and parents is usually not possible.

In assessing detection bias, blinding of the outcome assessors and data analysts needs to be considered. The outcome assessors in the study are usually the parents (who determine whether the child is dry or not). As mentioned previously, they are usually blinded

in drug-drug and drug-placebo studies. Blinding of data analysts, however, is usually not mentioned. Overall, the blinding strategies for the trials included in this review were unsatisfactory.

Incomplete outcome data

In 15 trials the trialists mentioned that some children had dropped out either before allocation to groups or at follow up, but this did not seem to be related to group allocation (Breger 1961; Breger 1962; Forrester 1964; Forsythe 1972; Gjessing 1968#; Harrington 1960#; Khosroshahi 1989; Leys 1956; Moltke 1979; Petersen 1974#; Shaffer 1978#; Sumner 2006; Tahmaz 2000; Wallace 1969; Wright 1974). Data have, therefore, been presented as reported in the trials. The majority of the trials had a low rate of attrition. This is probably because of the small size of the included sample.

Selective reporting

Given a low attrition rate, most trials did not report an intention-to-treat analysis. The authors believe that reporting bias is not expected to be of importance in this review.

Other potential sources of bias

Baseline recording of wetting

Eighteen of the 40 trials did not report a baseline estimate of the severity of bedwetting. Of these, 11 trials failed to include, or failed to record whether they included, a baseline period of observation of wetting before beginning the trial period (Al-Waili 1986#; Batislam 1995; Forrester 1964; Forsythe 1972; Kennedy 1968; Khosroshahi 1989; Kline 1968; Marconi 1985; Petersen 1974#; Salmon 1973#; Wallace 1969). In 12 trials, the randomised groups were stated to be comparable at baseline (Breger 1961; Dubow 1966; Forsythe 1972; Ingle 1968; Leys 1956; Tahmaz 2000; Varan 1996; Wallace 1969; Austin 2008; el-Sadr 1990a; Gelotte 2009; Van Hoeck 2008). In five trials there seemed to be baseline differences or unexplained differences in the numbers allocated to groups (Batislam 1995; Harrington 1960#; Mayon-White 1956; Sumner 2006; Wright 1974). The children in the 12 crossover trials acted as their own controls, although the washout period may have impacted on baseline wetting. Baseline comparability was not mentioned in the remaining 11 trials.

In the 10 new trials added in this update, three were crossover trials (Alawwa 2010#; Korczyn 1979#; Neveus 2008#). In three others the amount of wetting at baseline was reported to be comparable (Austin 2008; Esmaeili 2008; Gelotte 2009).

Organic causes and daytime wetting

In this update, we have chosen to include trials with participants who had daytime wetting as long as the trials were focused (partially or wholly) on nocturnal enuresis. In 26 trials, there was no specific mention of daytime symptoms in trial participants, while 15 trials specifically excluded children with daytime wetting. All trials included in the review had excluded children with organic diseases other than daytime wetting presumably due to functional bladder dysfunction. In one trial some children had an attention-deficit or hyperactivity disorder (Sumner 2006).

Previous treatment and setting

Three trials stated that none of the children had had previous treatment for their bedwetting (Batislam 1995; Gjessing 1968#; Sener 1998). In five trials some or all of the children had received previous treatment (Al-Waili 1989#; Harrington 1960#; Ingle 1968; Mayon-White 1956; Petersen 1974#) although it is likely that children in the other trials, which took place in hospital clinics (and which did not mention previous treatment), had failed simple management at home. In six trials some or all of the children were identified in the community or from school surveillance (Breger 1961; Breger 1962; Forrester 1964; GP Research Gp 1970#; Leys 1956; Shaffer 1978#). Two trials included children from children's homes or who had special needs (Kennedy 1968; Leys 1956).

Crossovers

Twelve trials had a crossover design (Alawwa 2010#; Al-Waili 1986#; Al-Waili 1989#; Gjessing 1968#; GP Research Gp 1970#; Harrington 1960#; Korczyn 1979#; Kunin 1970#; Neveus 2008#; Petersen 1974#; Salmon 1973#; Shaffer 1978#).

Of the 12 crossover trials four did not have a washout phase between the treatment arms. In five trials there was no mention of a washout phase. In only three trials a washout phase was used between the two arms (Kunin 1970#; Alawwa 2010#; Neveus 2008#),

and one had evidence of a carryover effect (Harrington 1960#). It was not possible to calculate generic inverse variances. In one trial data were available from the first arm only (GP Research Gp 1970#).

Age

In eight trials some children under the age of five years were included (Dubow 1966; Gjessing 1968#; Kline 1968; Mayon-White 1956; Moltke 1979; Shaffer 1978#; Wallace 1969; Wright 1974) and one trial included one adult (Harrington 1960#).

Provision of follow-up data

Only eight trials reported data after the treatment was ceased (Dubow 1966; el-Sadr 1990a; Esmaeili 2008; Ingle 1968; Leys 1956; Tahmaz 2000; Van Hoeck 2008). This reduces the strength of the conclusions that can be drawn from this review since the ICCS has now recommended that a follow-up of at least six months is necessary to report continued success (Neveus 2006).

Quality of data

Nine trials provided continuous data without measures of dispersion (Breger 1961; GP Research Gp 1970#; Leys 1956; Mayon-White 1956; Moltke 1979; Petersen 1974#; Shaffer 1978#; Sumner 2006; Wright 1974); these data have been presented in 'Data and analyses' tables.

In three trials continuous data had to be estimated by measurement of graphical data (Austin 2008; Marconi 1985; Wright 1974).

Effects of interventions

The effects of interventions have been described under four categories: drug versus placebo (1), drug versus drug (2), drug versus behavioural intervention (3) and different doses of drug (4). Whenever possible, we have attempted to synthesise data, resulting in nine meta-analyses involving 11 trials.

1. Drugs versus placebo (Analysis 01, Data and analyses table 01)

Thirty one trials compared an active drug with a placebo:

NSAIDs

- diclofenac plus imipramine (Batislam 1995);
- indomethacin (Al-Waili 1989#; Sener 1998);
- diclofenac (Al-Waili 1986#; Batislam 1995; Natchin 2000);

Psychoactive Drugs

- phenmetrazine (Harrington 1960#);
- chlorprothixene (Gjessing 1968#);
- meprobamate (Breger 1961);
- hydroxyzine (Breger 1962);
- chlordiazepoxide plus amitriptyline (Forsythe 1972);
- piracetam (Khosroshahi 1989);
- emepronium (Cetepin), (Petersen 1974#);
- diazepam (Kline 1968);
- propantheline (Leys 1956; Wallace 1969); propantheline (Mayon-White 1956);
- amphetamine plus ephedrine plus atropine (Wright 1974);

- oxazepam (Serenid) ([Salmon 1973#](#));
- chlordiazepoxide (Librium) ([Salmon 1973#](#));
- indoramin ([Shaffer 1978#](#));

Anticholinergic Drugs

- tolterodine ([Austin 2008](#); [Neveus 2008#](#)).
- oxybutynin ([Tahmaz 2000](#); [Van Hoeck 2008](#));
- atropine plus ephedrine ([Dubow 1966](#));

Others

- methylphenidate ([Breger 1962](#));

- furosemide ([Moltke 1979](#));
- atomoxetine ([Sumner 2006](#));

Compared with placebo, the groups receiving indomethacin, diclofenac and diazepam were better in terms of fewer wet nights during treatment:

- indomethacin WMD -3.09, 95% CI -4.23 to -1.96 ([Analysis 1.1.2](#); [Figure 4](#)) ([Al-Waili 1989#](#); [Sener 1998](#));
- diclofenac WMD -4.21, 95% CI -5.76 to -2.66 ([Analysis 1.1.3](#); [Figure 4](#)) ([Al-Waili 1986#](#)); and
- diazepam WMD -4.87, 95% CI -6.25 to -3.49 ([Analysis 1.1.4](#); [Figure 4](#)) ([Kline 1968](#)).

Figure 4. Forest plot of comparison: 1 Drugs versus placebo, outcome: 1.1 Number of wet nights per week.

Figure 4. (Continued)

-4 -2 0 2 4
favours drug favours placebo

Furthermore, the following drugs were better than placebo in terms of the number of children failing to achieve 14 dry nights during active treatment:

- indomethacin suppository RR 0.36, 95% CI 0.16 to 0.79 ([Analysis 1.3.2](#)) ([Al-Waili 1989](#));
- diazepam RR 0.22, 95% CI 0.11 to 0.46 ([Analysis 1.3.12](#)) ([Kline 1968](#));
- mesterolone RR 0.32, 95% CI 0.17 to 0.62 ([Analysis 1.3.17](#)) ([el-Sadr 1990a](#)); and
- atomoxetine RR 0.81, 95% CI 0.70 to 0.95 ([Analysis 1.3.14](#)) ([Sumner 2006](#)).

Meta analysis

We were able to combine data (subtotals only) for four treatments. Outcomes of two studies were pooled to estimate that indomethacin suppository reduced the bedwetting by 3 nights/fortnight (MD -3.09, 95% CI -4.23 to -1.96, [Analysis 1.1.2](#)). Similarly, diclofenac appeared to reduce the number not achieving 14 dry nights albeit with high heterogeneity ($I^2 = 90\%$). The statistical significance of the effect disappeared when a random-effects model was applied (RR 0.62, 95% CI 0.34 to 1.13, [Analysis 1.3.3](#)).

Several of the new trials added to this review concerned the use of anticholinergic medications (oxybutynin and tolterodine). They were used as a primary, stand alone therapy ([Neveus 2008](#); [Tahmaz 2000](#)) ([Analysis 1.3](#)) or in combination with other established therapies such as alarms ([Van Hoeck 2008](#)) ([Analysis 1.3.20](#)) or desmopressin ([Austin 2008](#)) ([Analysis 1.3.16](#)).

Only five trials reported information about relapse rates once treatment had stopped ([Dubow 1966](#); [el-Sadr 1990a](#); [Forsythe 1972](#); [Tahmaz 2000](#); [Van Hoeck 2008](#)). None of the medications tested were better than placebo in preventing relapse ([Analysis 1.4](#)). In a trial with long follow-up, addition of oxybutynin did not reduce relapse rates compared to enuresis alarms alone ([Van Hoeck 2008](#); [Analysis 1.4.5](#)).

The other trials were too small to provide reliable information or did not provide useable data.

2. Drug to drug comparisons (Analysis 02, Data and analyses table 02)

Nineteen trials compared one active drug with another:

- diclofenac with imipramine or imipramine plus diclofenac ([Batislam 1995](#));

- meprobamate plus hydroxyzine with imipramine ([Ingle 1968](#));
- ephedrine with imipramine ([Kunin 1970](#));
- indomethacin with desmopressin ([Sener 1998](#));
- oxybutynin with pseudoephedrine ([Varan 1996](#));
- oxybutynin with indomethacin ([Varan 1996](#));
- pseudoephedrine with indomethacin ([Varan 1996](#));
- hydroxyzine with methylphenidate ([Breger 1962](#));
- triclofos with ephedrine ([GP Research Gp 1970](#));
- oxybutynin with dicyclomine ([Marconi 1985](#));
- diclofenac with desmopressin ([Natochin 2000](#));
- oxybutynin with imipramine ([Tahmaz 2000](#), [Esmaeili 2008](#));
- oxybutynin with oxybutynin plus imipramine ([Tahmaz 2000](#), [Esmaeili 2008](#));
- oxybutynin with oxybutynin plus desmopressin and imipramine ([Lee 2005](#));
- tolterodine with imipramine ([Neveus 2008](#));
- propantheline with propantheline plus phenobarbitone ([Wallace 1969](#));
- furosemide with imipramine ([Moltke 1979](#));
- emepronium with imipramine or imipramine-N-oxide ([Petersen 1974](#)); and
- indoramin ([Shaffer 1978](#)).

Comparisons with tricyclics

In single small trials:

- imipramine was significantly better during treatment than meprobamate ([Ingle 1968](#)), tolterodine ([Neveus 2008](#)) and ephedrine ([Kunin 1970](#)) ([Analysis 2.1](#)); and
- in two small trials which did not provide standard deviations, imipramine resulted in fewer wet nights than furosemide ([Moltke 1979](#)) and emepronium ([Petersen 1974](#)) ([Analysis 2.2](#)).

However, the trials did not provide reliable information about relapse rates after treatment stopped.

Comparisons with desmopressin

In one small trial with 62 children, desmopressin was better than diclofenac in terms of achieving 14 dry nights during treatment (RR 1.94, 95% CI 1.13 to 3.33, [Analysis 2.3.4](#); [Figure 5](#)) ([Natochin 2000](#)). In another, desmopressin was better than indomethacin (MD for wet nights during treatment 1.45, 95% CI 0.53 to 2.37, [Analysis 2.1.3](#)) ([Sener 1998](#)).

Figure 5. Forest plot of comparison: 2 Drug - drug comparisons, outcome: 2.3 Number not achieving 14 consecutive dry nights.

Figure 5. (Continued)

Comparisons with anticholinergic medications

Several of the new trials added to this updated review concerned the use of anticholinergic medications (oxybutynin and tolterodine). Small trials which investigated the use of oxybutynin alone (Esmaeili 2008; Tahmaz 2000) and in combination with imipramine (Esmaeili 2008; Tahmaz 2000) or tolterodine (Neveus 2008#) have been reported.

A combination of oxybutynin and imipramine was more effective in terms of number of wet nights when compared to imipramine alone (MD -2.1, 95% CI -2.99 to -1.21, Analysis 2.1.12). Similarly, oxybutynin alone was less effective than combination therapy of oxybutynin and imipramine (MD 1.1, 95% CI 0.27 to 1.93, Analysis 2.1.11).

A combination of imipramine and oxybutynin was also more effective than monotherapy with either drug in terms of the number of children failing to achieve 14 dry nights:

- oxybutynin + imipramine versus oxybutynin RR 1.46, 95% CI 1.06 to 2.01 (Analysis 2.3.6; Figure 5);
- imipramine versus oxybutynin + imipramine RR 0.68, 95% CI 0.50 to 0.94 (Analysis 2.3.8; Figure 5).

The rate of failure or relapse during follow up was also lower with the combination of imipramine and oxybutynin than monotherapy with either drug:

- oxybutynin versus imipramine + oxybutynin RR 2.01, 95% CI 1.23 to 3.28 (Analysis 2.4.3);
- oxybutynin + imipramine versus imipramine RR 0.35, 95% CI 0.16 to 0.77 (Analysis 2.4.4).

Oxybutynin did not appear to enhance the effect of desmopressin but the trial was small (Lee 2005) (Analysis 2.3.11; Figure 5).

- Children had fewer wet nights while taking oxybutynin compared with dicyclomine (Analysis 2.1.6) but follow-up data were not provided (Marconi 1985). The other trials were too small to provide reliable information.

3. Drugs versus behavioural interventions (Comparison 03, Data and analyses table 03)

Six trials included a behavioural or other non-drug intervention for bedwetting: an alarm compared with amphetamine (Forrester 1964); an alarm with methedrine supplementing the alarm (Kennedy 1968); an alarm with amphetamine or ephedrine plus atropine (Wright 1974); oxybutynin and acupressure (Yukse 2003), and with a play-and-supportive therapy intervention (Khosroshahi 1989). The small sample size was a classic feature of these trials (average 36 participants per trial). Alarms were found to be 2 to 3.5 times more effective than the medications in reducing the number of children not achieving 14 dry nights. They were found to be superior to amphetamine (RR 2.2, 95% CI 1.12 to 4.29); oxybutynin (RR 3.25, 95% CI 1.77 to 5.98) and oxybutynin plus holding exercises (RR 3.3, 95% CI 1.84 to 6.18). There was no difference in efficacy of oxybutynin and acupressure (RR 0.7, 95% CI 0.41 to 1.20). None of these trials reported relapse rates.

4. Higher versus lower doses of drugs (Comparison 04)

No trials were found which compared different doses of the same drug.

5. Combination therapy versus monotherapy (Comparison 05)

Five studies investigated whether supplementary therapy with oxybutynin or other anticholinergics improved the efficacy of treatment. Four studies involved oxybutynin (Esmaili 2008; Lee 2005; Tahmaz 2000; Van Hoeck 2008) while one tested tolterodine (Austin 2008). Anticholinergic therapy was used in conjunction with desmopressin (Austin 2008; Lee 2005), imipramine (Esmaili 2008; Tahmaz 2000) and alarms (Van Hoeck 2008). The studies reported varying durations of treatment (one to six months) and follow-up (none to 12 months). Four studies only included children with monosymptomatic nocturnal enuresis (Austin 2008; Esmaili 2008; Tahmaz 2000; Van Hoeck 2008) while one reported the effects in monosymptomatic and nonmonosymptomatic nocturnal enuresis (Lee 2005).

During treatment, only the combination of oxybutynin with a tricyclic drug was better than the tricyclic alone (RR 0.68, 95% CI 0.50 to 0.92, Analysis 5.1.3; Figure 6). This benefit persisted after treatment stopped (RR 0.48, 95% CI 0.31 to 0.74, Analysis 5.2; Figure 7). There was no additive effect during treatment when oxybutynin was added to an alarm, but the single trial was small (Analysis 5.1.4) (Van Hoeck 2008). Nor did an anticholinergic appear to enhance the action of desmopressin during treatment in two small trials (Analysis 5.1.1 and Analysis 5.1.2) (Austin 2008; Lee 2005).

Figure 6. Forest plot of comparison: 5 Combination therapy versus monotherapy, outcome: 5.1 Number not achieving 14 dry nights.

Figure 7. Forest plot of comparison: 5 Combination therapy versus monotherapy, outcome: 5.2 Number failing or relapsing after end of treatment.

Adverse effects

Nineteen trials mentioned adverse effects but not all gave detailed information about how many children or which trial arms were affected.

Studies involving NSAIDs

- An indomethacin suppository was associated with mild rectal burning in one trial (Al-Waili 1989#).
- Mild gastrointestinal symptoms were mentioned in a trial of imipramine and diclofenac, but it was not clear which treatment was responsible (Batislam 1995).
- Five children withdrew because of adverse events (2 assigned to ibuprofen-pseudoephedrine, 2 assigned to pseudoephedrine, and 1 assigned to ibuprofen). Adverse events reported by more than 1 child in a treatment group were headache (5%), infection (3%), abdominal pain (2%), fever (2%), cough increased (2%), taste perversion (1%), vomiting (1%), diarrhea (1%), and gastroenteritis (1%). (Gelotte 2009)

Studies involving tricyclics

- Mild gastrointestinal symptoms were mentioned in a trial of imipramine and diclofenac, but it was not clear which treatment was responsible (Batislam 1995).
- Imipramine, imipramine-N-oxide or emepronium may have been associated with nausea, decreased appetite, sleep disturbance, rash, headaches, sweating, fatigue, sullenness or tremor (Petersen 1974#).
- Nine patients experienced side effects during imipramine treatment (three slight mood change, two insomnia, one palpitations, two slight nausea and one child interrupted medication because of intense nausea) (Neveus 2008#).

Studies involving anticholinergics

- An atropine and ephedrine mixture resulted in dry mouth, insomnia, blurred vision, dizziness, constipation, nervousness and flushing (Dubow 1966).

- Oxybutynin was associated with visual disturbances, xerostomia, digestive disturbances, nausea, vertigo or tachycardia (Marconi 1985).
- One child had side effects (slight mood change) with tolterodine (Neveus 2008#).

Other drugs

- An atropine and ephedrine mixture resulted in dry mouth, insomnia, blurred vision, dizziness, constipation, nervousness and flushing (Dubow 1966).
- When amphetamine resulted in sleeplessness or restlessness, the dose needed to be reduced or stopped; in another trial amphetamine was also used for some children who slept too deeply to be wakened by the bell from the alarm (Forrester 1964).
- Chlorproxitine was associated with drowsiness (Gjessing 1968#).
- Meprobamate, hydroxyzine or imipramine may have caused a burning sensation in two children (Ingle 1968).
- Piracetam may have caused mild headache or nausea (Khosroshahi 1989).
- During diazepam treatment, drowsiness and ataxia were severe enough to cause one child to discontinue, but one other child on placebo treatment stopped because of insomnia and hyperactivity (Kline 1968).
- Children given dicyclomine reported tachycardia and headache but these were not serious enough to discontinue treatment (Marconi 1985).
- Imipramine, imipramine-N-oxide or emepronium may have been associated with nausea, decreased appetite, sleep disturbance, rash, headaches, sweating, fatigue, sullenness or tremor (Petersen 1974#).
- Imipramine and oxybutynin were associated with dry mouth or nausea but these were also reported during placebo treatment (Tahmaz 2000).
- Oxybutynin resulted in epistaxis, flushing or voiding difficulty; indomethacin in gastrointestinal irritation; and no adverse effects were reported for pseudoephedrine (Varan 1996).

- Toxic adverse effects resulting in dropout were reported for propantheline (headache, dry mouth) and propantheline plus phenobarbitone (headache, dry mouth, skin rash) but some children on placebo also had headache, abdominal pain or vertigo, which did not result in dropout (Wallace 1969). In another trial of propantheline, children on both active and placebo treatment reported dry mouth (Mayon-White 1956).
- Heart rate was increased in the atomoxetine-treated group (by a mean of 11 beats per minute compared with placebo, and episodes of an increase rate of 20 beats per minute in 6/44 children compared with none in the placebo group) (Sumner 2006). Children also reported more headaches, nausea, decreased appetite, gastroenteritis, insomnia, irritability and pyrexia with atomoxetine treatment, although none reached statistical significance compared with placebo. The rate of discontinuation due to adverse effects in the two groups were similar (2/44 versus 1/43 on placebo).

Five other trials mentioned specifically that there were no adverse effects (diclofenac in Al-Waili 1986#; diclofenac and desmopressin in Natochin 2000; and indomethacin and desmopressin in Sener 1998; hydrochlorthiazide in Alawwa 2010#); and tolterodine plus desmopressin in Austin 2008). The remaining 17 trials did not mention adverse effects.

DISCUSSION

Summary of main results

Comparisons with placebo

Only five of the drugs were superior to placebo (indomethacin, diclofenac, diazepam, mestrolone and atomoxetine) (Analysis 1.1; Analysis 1.3; Figure 4; Figure 3) during treatment, both in terms of fewer wet nights and less not achieving 14 consecutive dry nights; but none of the reported drugs were effective in reducing the relapse rates when the treatment was withdrawn (Dubow 1966; el-Sadr 1990a; Forsythe 1972; Tahmaz 2000; Van Hoeck 2008). In the remaining drug comparisons with placebo the numbers were too small to draw reliable conclusions and none of the drugs, except oxybutynin, are currently used in practice for children with enuresis. Most practitioners would be reluctant to prescribe major psychoactive drugs (for example chlorthalidopoxide, amphetamine and diazepam) for children when alternative, effective treatments with fewer adverse effects are available. At present, the mechanisms behind the effect of psychoactive drugs in children with nocturnal enuresis are uncertain.

Two interesting trials (Austin 2008; Neveus 2008#) included children who did not respond to primary therapy for enuresis. Both these trials used tolterodine, a newer anticholinergic medication. When combined with desmopressin (Austin 2008) it did not yield any additional benefit.

Comparisons with other drugs

Desmopressin was better than for indomethacin (WMD for wet nights during treatment 1.45, 95% CI 0.53 to 2.37) (Sener 1998); and diclofenac (RR for failure to achieve 14 dry nights 1.94, 95% CI 1.13 to 3.33) (Natochin 2000) suggesting that indomethacin and diclofenac would not be appropriate treatments for children with enuresis. Today, neither is in fact prescribed for this indication.

Similarly the results for imipramine were better than those for meprobamate, ephedrine, furosemide and emepronium, but again there was no information after stopping the drugs. These drugs are also not used in current practice for children with enuresis.

The results of combining oxybutynin with imipramine appear to be encouraging. The combination out-performs imipramine monotherapy in achieving short term as well as long term success (Analysis 2.3.14; Analysis 2.4; Figure 5). The reasons behind this findings could be attributed to some of the children having 'unreported' non-monosymptomatic nocturnal enuresis that is associated with daytime lower urinary tract symptoms. This may provide a useful lead in designing future trials which incorporate children, especially those with non-monosymptomatic enuresis.

Only seven studies provided data on the relapse rates when the drug was withdrawn (Dubow 1966; el-Sadr 1990a; Esmaeili 2008; Forsythe 1972; Ingle 1968; Tahmaz 2000; Van Hoeck 2008). Apart from the combination therapy with anticholinergics reported above, no other drug was effective in reducing the relapse rates when the treatment was withdrawn.

Comparisons with behavioural treatments

There was little reliable information about drugs compared with behavioural treatments except that enuresis alarm therapy was better than amphetamine during treatment. No trials presented data describing results after stopping treatment.

Adverse effects

Of the drugs which were more effective than placebo (indomethacin, diclofenac and diazepam), adverse effects were reported for indomethacin, diazepam, atomoxetine and possibly for diclofenac, which was used in combination with imipramine.

In summary, desmopressin, tricyclics and enuresis alarm therapy were better than any of the drugs with which they were compared in this review, but the trials were all small or did not provide follow-up data and therefore it is uncertain whether treatment response was sustained. There was not enough evidence to suggest that any of the other drugs tested were effective or suitable for children. The lack of evidence for the effectiveness of the drugs tested needs to be viewed in the context of better long term results using other interventions. Further trials comparing drugs with each other (specifically desmopressin, which seems to be as effective as tricyclics but with fewer adverse effects) (Glazener 2002; Glazener 2003a) and in combination therapy with effective behavioural interventions such as alarms (Glazener 2005a) would be helpful in determining the place of pharmacotherapy for children with enuresis.

Overall completeness and applicability of evidence

This review identified a large number of studies which tested a variety of drugs as primary therapy for nocturnal enuresis. More than 30 classes of drugs have been tested, none with any success. The review involves over 2300 participants, albeit spread out over a large number of small trials. This may weaken any strength of recommendations the authors are able to make.

It is apparent that most drugs that have been tested have side effects and poor efficacy. The only exception to this rule appears to be anticholinergic drugs when used in conjunction with established treatments like imipramine. They appear to improve the short term

efficacy as well as reduce the relapse rates. This finding provides only limited support for their ongoing use in practice as it needs to be tested in further research before being adopted into clinical practice.

Quality of the evidence

The 40 trials (including 12 crossover trials) which were included in this updated review were mostly small and of poor quality. The average number of children per trial (62) was lower than in other Cochrane reviews (Mallett 2002). The small sample sizes resulted in wide confidence intervals and imprecision which could obscure or over estimate underlying treatment effects. None of the trials satisfied all of the quality criteria. The trials appeared to be especially weak in the randomisation of participants and in blinding the outcome assessor (Figure 2). In most of the manuscripts, these aspects were not covered in adequate details leading to uncertainty. The majority of the trials had very low attrition; this could be partly due to their small sample size. There were only four trials which had adequate randomisation, and eight which had adequate allocation concealment.

Most of the comparisons were addressed only in single trials, precluding meta-analysis. Only three drugs were tested in more than one trial (indomethacin suppository versus placebo (Al-Waili 1989#; Sener 1998); and diclofenac versus placebo (Al-Waili 1986#; Batislam 1995; Natchin 2000) and oxybutynin (Esmaeili 2008; Tahmaz 2000). Two each of these trials were of crossover design (Al-Waili 1986#; Al-Waili 1989#).

Most trials recruited children from enuresis clinics or hospitals; only seven included some or all children from the community, and only two were amongst institutionalised children or those with special needs. One trial was clearly industry funded (Sumner 2006) and reported methodological problems such as baseline differences between the groups.

The ICCS defined continued success as no relapse after six months and cure as no relapse two years after withdrawing treatment (Neveus 2006). Insufficient follow-up data in the trials affects the strengths of recommendations of this review. Only 13 trials have reported any follow-up data, of which only four have a follow up of six months or more, the longest being 13 months.

Other potential biases included inadequate baseline information about participants, especially on the severity of bedwetting (13 trials). With the recognition by ICCS of the two forms of nocturnal enuresis (Neveus 2006), treatment response to drugs other than desmopressin and tricyclics may vary. The majority of the trials (26) were ambiguous regarding the presence or absence of daytime wetting or other daytime urinary symptoms in their participants. Ten trials specifically excluded children with daytime wetting.

Potential biases in the review process

Despite best efforts, some published literature may have been missed. The quality assessment was based on the published manuscripts. This may have unintentionally downgraded the perceived quality of blinding and allocation concealment. Given the absence of trial registration for most of the trials included in this review, bias due to selective reporting of outcomes was difficult to ascertain.

AUTHORS' CONCLUSIONS

Implications for practice

There was not enough evidence to judge whether or not the included drugs cured bedwetting permanently. There was limited evidence to suggest that desmopressin, imipramine and enuresis alarm therapy were better than the drugs to which they were compared. In other reviews, desmopressin, tricyclics and alarm interventions have been shown to be effective. There was also weak evidence to suggest that combination therapy with anticholinergic therapy might increase the efficacy of tricyclics.

Implications for research

Further research on alternative drugs for enuresis must incorporate comparisons with proven effective treatments such as desmopressin and tricyclic drugs; alarms; or other behavioural interventions such as lifting, waking and reward systems. Placebo controlled drug trials without incorporating established therapies should be discouraged when proven effective therapies are available. The role of anticholinergics as a supplementary therapy in nocturnal enuresis should be studied further.

The trials should make conscious efforts to adopt the nomenclature guidelines prescribed by the ICCS. Children with nocturnal enuresis should be included irrespective of whether they have monosymptomatic or non-monosymptomatic nocturnal enuresis, which will increase the broad applicability of results. Subgroup analysis of monosymptomatic and non-monosymptomatic groups may provide further knowledge about the drug effectiveness.

Trials need to be of a larger size to minimise imprecision. Trials need to report on follow-up data, as prescribed by the ICCS. A minimum follow-up of six months should be factored into the trials in order to give some estimate to success and cure in the long term (Neveus 2006). They should use uniform outcome measures such as the number of wet nights during treatment and after the end of treatment; the number of children achieving 14 consecutive dry nights; adverse effects; and relapse rates after treatment. Trialists should ensure that the methodological quality of the trials is high in order to minimise bias.

Further research is needed to determine which interventions are appropriate for which groups and in which circumstances (for example as a short term measure to cover nights away from home) in order to guide choice of treatment.

ACKNOWLEDGEMENTS

This review was based on an updated review by Cathryn Glazener from the University of Aberdeen, Jonathan Evans from Nottingham University Hospitals NHS Trust and Rachel E Peto from the University of York, UK. Their review was based on one originally written by the NHS Centre for Reviews and Dissemination, University of York, UK. The original authors were Deborah Lister-Sharp, Susan O'Meara, Matthew Bradley and Trevor A Sheldon. It is published as: A Systematic Review of the Effectiveness of Interventions for Managing Childhood Nocturnal Enuresis, CRD Report 11, NHS Centre for Reviews and Dissemination, University of York (Lister-Sharp 1997). The York reviewers obtained information from a variety of sources, including organisations, manufacturers and individuals. These are listed in the NHS Centre for Reviews and

Dissemination Report ([Lister-Sharp 1997](#)), and we acknowledge their contribution to this review.

We would like to thank Professor Cathryn Glazener, Sheila Wallace, June Cody and Dr Muhammad Imran Omar from the Cochrane Incontinence Review Group, Aberdeen UK, for their tireless help and advice in conducting this update.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Al-Waili 1986#

Methods	RCT (double-blind crossover trial) Systematic baseline measure of wetting: No Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: Teaching hospital, Baghdad
Participants	No. of children (boys): 20 (6) Incl: primary enuresis, every night Excl: asthma, renal and gastrointestinal disorders, hypersensitivity to NSAIDs Age: 6-17 years (mean 10)
Interventions	A (20): diclofenac sodium 50 mg orally B (20): placebo Duration of treatment: 30 days each arm Follow up: none Non-responders treated with 75 mg diclofenac for 30 more days
Outcomes	Mean DRY nights (SEM): A: 21.7 (1.4), B: 3.65 (3.1) = mean (SD) wet nights per week: A: 1.94 (1.47), B: 6.15 (3.22) No. with at least 14 wet nights in 30: A: 5/20, B: 18/20 Adverse events: none
Notes	Diclofenac sodium is a prostaglandin synthesis inhibitor No washout Groups comparable at baseline (as crossover trial)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Method not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Reported as "double-blind", however it is not specified who was blinded.
Blinding (performance bias) - care givers All outcomes	Unclear risk	Reported as "double-blind", however it is not specified who was blinded.

Al-Waili 1986# (Continued)

Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	insufficient information
Other bias	Unclear risk	No washout period

Al-Waili 1989#

Methods	RCT (double-blind crossover trial) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: Outpatient clinic, teaching hospital, Baghdad	
Participants	No. of children (boys): 19 (7) Incl: primary nocturnal enuresis, failed previous treatment Excl: asthma, renal and gastrointestinal disorders, hypersensitivity to drugs Previous treatment: antispasmodics, fluid restriction, imipramine, all stopped 2 months before trial Age: mean 9 years (range 6-15) Baseline wetting: every night	
Interventions	A (19): indomethacin suppository 50 mg B (19): placebo Duration of treatment: 30 days Follow up: if not cured, continued with 100 mg indomethacin unblinded	
Outcomes	Mean DRY nights during trial (SD): A: 19.5 (10.5), B: 3.6 (5.7) = mean wet nights per week: A: 2.45 (2.45), B: 6.16 (1.33) No. not achieving 10 dry nights: A: 5/19, B: 14/19 Adverse events: A: mild rectal burning sensation	
Notes	Groups comparable at baseline as crossover No washout	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were selected randomly
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Reported as "double-blind", however it is not specified who was blinded.

Al-Waili 1989# (Continued)

Blinding (performance bias) - care givers All outcomes	Unclear risk	Reported as "double-blind", however it is not specified who was blinded.
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	No washout

Alawwa 2010#

Methods	Crossover RCT Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Conducted in urology clinics
Participants	No. of children (boys): (40 but 8 excluded), 32 (17) Incl: primary nocturnal enuresis; at least 3 wet nights /week Excl: organic causes Previous Rx: not mentioned, but stopped 2 weeks prior Age: 6-18 y
Interventions	Hydrochlorthiazide versus placebo Duration of treatment: 3 months each with 2 weeks wash out Follow up: none
Outcomes	No. not achieving 14 dry nights during trial: HCTZ: 33/32, PL: 32/32
Notes	Very few outcomes reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not specified
Blinding (performance bias) - participants All outcomes	Unclear risk	Not mentioned

Alawwa 2010# (Continued)

Blinding (performance bias) - care givers All outcomes	Unclear risk	Not mentioned
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 patients excluded but exclusion not related to outcome
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis
Other bias	Low risk	Very few outcomes reported, washout period planned

Austin 2008

Methods	Design RCT Systematic baseline measure of wetting YES Organic causes excluded YES Daytime wetting specifically excluded? YES Setting/recruitment: Pt referred to urology clinic for NE
Participants	Number of subjects (boys) 48 (24) Number of dropouts: 14 (7 refused consent, 7 non compliant) Inclusion criteria: Monosymptomatic PNE desmopressin non-responders (Min 4 wet night per week on desmopressin) Exclusion criteria: LUT symptoms or bowel dysfunction, pt on anticholinergics or contraindication for anticholinergics Ages: 6-17 years Baseline wetting A. 6.56 +/- 0.81 wet nights per week, B. 6.22 +/- 1.16
Interventions	A (18) Desmopressin + Tolterodine LA B (16) Desmopressin + Placebo Duration of treatment: 1 month Duration of follow up: 1 month (no follow up beyond end of treatment)
Outcomes	Mean wet nights during trial: A 3/7 versus 5/7 (from figure 2) No. not achieving 14 dry nights during trial: A. 15/18=83% vs B. 15/16 (94%) No. not achieving 14 dry nights during trial or relapsing after: (same as above) Mean wet nights after end of trial (same as above) Adverse events (numbers and details): reported as none

Austin 2008 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Stratified randomisation used
Allocation concealment (selection bias)	Unclear risk	not mentioned
Blinding (performance bias) - participants All outcomes	Low risk	Blinded. Patients received an unlabeled bottle of either tolterodine extended-release capsules or matching placebo capsules. Patients were asked to take 1 capsule each night, with their full dose of desmopressin therapy (0.6 mg total per night), for 4 weeks.
Blinding (performance bias) - care givers All outcomes	Low risk	Blinded. Patients received an unlabeled bottle of either tolterodine extended-release capsules or matching placebo capsules. Patients were asked to take 1 capsule each night, with their full dose of desmopressin therapy (0.6 mg total per night), for 4 weeks.
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients reported, 14 dropouts
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis 14/48 did not participate
Other bias	Low risk	Side effects mentioned

Batislam 1995

Methods	RCT Systematic baseline measure of wetting: No Organic causes excluded: Yes Daytime wetting excluded: Not mentioned
Participants	No. of children (boys): 78 (48) Incl: primary nocturnal enuresis; at least 3 wet nights /week Excl: organic causes Previous Rx: none Age: 6-18 y
Interventions	A (16): imipramine 1mg/kg/day B (20): diclofenac sodium C (30): imipramine + diclofenac D (12): placebo Duration of treatment: 4 weeks Follow up: 1 and 3 months
Outcomes	No. improving >50%: A: 2/16, B: 4/20, C: 2/30, D: 6/12

Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) (Review)

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Batislam 1995 (Continued)

No. relapsing: A: 6, B: 0, C: 4, D: 0

Adverse events: 8 had mild gastrointestinal symptoms, but not clear which groups

Notes	No useable data Unexplained difference in size of groups at allocation
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were divided at random into 4 groups
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Not mentioned
Blinding (performance bias) - care givers All outcomes	Unclear risk	Not mentioned
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	High risk	Baseline imbalance of numbers in treatment groups

Breger 1961

Methods	RCT (divided by random selection) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: children's psychiatric service, Johns Hopkins Hospital, Baltimore, referred by doctor or school
Participants	No. of children: 100 Dropouts: 33 Excl: organic uropathy, severe learning difficulties Age: 5-14 years Baseline wetting: A: 6.7 wet nights per week, B: 6.54
Interventions	A (34): meprobamate (3x/ day; dosage depends on age: 5-9 years = 200 mg; 10-14 years = 400 mg) B (33): identical placebo Duration of treatment: 3 months

Breger 1961 (Continued)

Follow up: none

Outcomes	Mean wet nights during trial: A: 3.26, B: 3.21 No. not achieving 14 dry nights during trial: A: 31/34, B: 27/33 Outcomes not different according to sex
Notes	No SDs No reprimands, no fluid restriction, no lifting Dropouts 'comparable from each group'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Cases were divided by random selection into two groups
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias) - participants All outcomes	Low risk	The capsules were identical in appearance and were coded by another member of the department. The code was unavailable to the experimenter until after the completion of the study.
Blinding (performance bias) - care givers All outcomes	Low risk	The capsules were identical in appearance and were coded by another member of the department. The code was unavailable to the experimenter until after the completion of the study.
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not clearly mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 67 patients who completed the study were included in the final analysis
Selective reporting (reporting bias)	Unclear risk	No intention-to-treat analysis
Other bias	Low risk	Adverse effects mentioned

Breger 1962

Methods	RCT (divided by random selection) Systematic baseline measure of wetting: Yes (but not fully reported) Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: children's psychiatric service, Johns Hopkins Hospital, Baltimore, referred by doctor or school
Participants	No. of children: 150 Dropouts: 26 Excl: organic uropathy, severe learning difficulty Age: 5-14 years Baseline wetting: 92/124 wet 7x/week; 32/124 wet less often
Interventions	A (41): hydroxyzine chloride age 5-9, 10 mg 2x/day; age 10-14 10-20 mg 3x/day

Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) (Review)

Breger 1962 (Continued)

B (44): methylphenidate hydrochloride (Ritalin) age 5-9 years 5 mg 2x/day; age 10-14 5-10 mg 3x/day
C (39): placebo

Duration of treatment: 3 months (minimum 2)

Follow up: None

Outcomes	No. not achieving 14 dry nights during trial: A: 33/41, B: 34/44, C: 38/39
Notes	Hydroxyzine is a tranquillizer, methylphenidate is a stimulant No reprimands, no fluid restriction, no waking

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Cases were divided by random into 3 groups
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Not clearly mentioned
Blinding (performance bias) - care givers All outcomes	Low risk	The code being unavailable to the experimenter until after the completion of the study
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not clearly mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	17% dropped out of the study prior to second month and not included in the analysis
Selective reporting (reporting bias)	Unclear risk	No intention to treat analysis
Other bias	Low risk	Adverse effects mentioned

Dubow 1966

Methods	RCT (double blind study) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: Paediatric Department, New York
Participants	No. of children (boys): 50 (28) Incl: enuresis Age: 4-15 years Baseline wetting: A: 4.64 wet nights, B: 5.4
Interventions	A (25): atropine sulphate 0.15 mg + ephedrine sulphate 7.5 mg: age <10 years = 2 tablets, > 10 = 4 tablets

Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) (Review)

Dubow 1966 (Continued)

B (25): matching placebo

Duration of treatment: 1 month

Follow up: 2 months, then all children received active treatment

Outcomes	No. not achieving 14 dry nights: A: 18/25, B: 18/25 Excellent or moderate improvement: A: 11/25, B: 17/25 Relapse or fail after trial: A: 23/25, B: 25/25 Adverse events: A: 6/25 (dry mouth, insomnia, blurred vision, dizziness, constipation, nervousness, flushing) B: 0/25 Side effects attributed to dose being too high
Notes	Groups comparable on baseline wetting All children also had extra fluids and bladder training during the day, fluid restriction at night, wakening, reward for dry nights

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias) - participants All outcomes	Low risk	Used identical tablets and blinding of participants was probably done.
Blinding (performance bias) - care givers All outcomes	Unclear risk	Double-blind study, probably patients and personnel were blinded
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	Side effects well reported

el-Sadr 1990a

Methods	Design RCT Systematic baseline measure of wetting NO Organic causes excluded YES Daytime wetting specifically excluded? YES
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el-Sadr 1990a (Continued)

Setting/recruitment – not mentioned

Participants	Number of subjects (boys) (30 boys) Number of dropouts: none Inclusion criteria: boys with primary NE, healthy, no daytime urinary problems or urological problems Exclusion Criteria: organic and neurological disease (spina bifida identified on X ray included) Ages 6-10 years Baseline wetting: none
Interventions	A (20) mesterolone 20mg daily for 14 days (androgen) B (10) placebo (vitamin C) Duration of treatment: 14 days Duration of follow up: 4 months after ceasing treatment
Outcomes	1. Wet nights on treatment = Mean wet nights at end of treatment – not given 2. # Not achieving 14 consecutive dry nights - fail = # not achieving 14 dry nights at end of treatment: A 6/20, B 10/10 3. Wet night after end of treatment = Mean wet nights at follow up – not given 4. # failed or relapsed after end of treatment = # not achieving 14 dry nights or relapsing at follow up (at 4 months): A 15/20 (assume B 10/10) 5. Wet nights on treatment no SD = # wet nights at end of treatment: not given Adverse events (numbers and details) – none reported

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Low risk	Identical coded containers used.
Blinding (performance bias) - care givers All outcomes	Unclear risk	Not mentioned
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up

el-Sadr 1990a (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported, Dysfunctional voiding symptom score and failure to achieve dry nights
Other bias	High risk	No adverse events reported

Esmaeili 2008

Methods	<p>RCT</p> <p>Systematic baseline measure of wetting: Yes</p> <p>Organic causes excluded: Yes</p> <p>Daytime wetting excluded: Yes</p> <p>Setting: Nephrology clinic, Iran</p>
Participants	<p>No. of children (boys): 112 (69)</p> <p>Number of dropouts -23 (poor compliance)</p> <p>Inclusion criteria – primary NE (at least 2 nights per week for past 3 months), no prior pharmacological treatments for enuresis in past month</p> <p>Exclusion criteria – voiding dysfunction, UTI, abn urinalysis, urological or neurological abnormalities</p> <p>Ages - 6-14 years</p> <p>Baseline wetting:</p> <p>A 4.9 ± 1.12 (mean wet nights per week)</p> <p>B 5.0 ± 1.1 (mean wet nights per week)</p> <p>C 5.4 ± 1.0 (mean wet nights per week)</p>
Interventions	<p>A (29) Imipramine</p> <p>B (26) Oxybutynin</p> <p>C (34) Imipramine + Oxybutynin</p> <p>Duration of treatment: 1 month</p> <p>Duration of follow up: 1 month after treatment</p>
Outcomes	<p>1. Wet nights on treatment = Mean wet nights at end of treatment</p> <p>A 3.5 ± 2 (mean wet nights per week)</p> <p>B 2.5 ± 1.7 (mean wet nights per week)</p> <p>C 1.4 ± 1.5 (mean wet nights per week)</p> <p>2. # Not achieving 14 consecutive dry nights - fail = # not achieving 14 dry nights at end of treatment</p> <p>A=25/29, B=20/26 C=20/34</p> <p>4. # Failed or relapsed after end of treatment = # not achieving 14 dry nights or relapsing at follow up</p> <p>A=13/22, B=9/21, C=6/29</p>

Esmaeili 2008 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Referral number used for randomisation
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Not mentioned
Blinding (performance bias) - care givers All outcomes	Unclear risk	Not mentioned
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Nearly 25% (23/112) lost to follow-up after randomisation
Selective reporting (reporting bias)	High risk	Intention-to-treat analysis not used.
Other bias	High risk	Adverse events not reported

Forrester 1964

Methods	RCT Systematic baseline measure of wetting: No Organic causes excluded: No Daytime wetting excluded: Not mentioned Setting: Children recruited from community survey
Participants	No. of children 118 (33 properly included in trial) Dropouts: 25 cured before trial, 32 improved, 9 not suitable, 15 defaulted, 4 received wrong intervention Incl: aged 8-14, wet at least once per week, suitable family circumstances Ages: 8-14 years
Interventions	A (16): Alarm (+ amphetamine for some children if not wakened by bell) B (17): Amphetamine 2.5 to 5mg, increasing weekly if no response, decreasing if response, stopped if sleepless or restless Duration of treatment: up to 6 months
Outcomes	No. not achieving 21 dry nights: A: 6/16, B: 14/17 Failure to comply with treatment properly: A: 4/17, B: 6/16
Notes	Successful treatment requires the families to understand the commitment involved

Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) (Review)

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Forrester 1964 (Continued)

Results including failure to comply in group as allocated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were listed in pairs for age and sex. One of each pair was marked A and the other B according to the lots drawn. All As received conditioning treatment and Bs amphetamine. This procedure was used to follow a random allocation of treatment.
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Not mentioned
Blinding (performance bias) - care givers All outcomes	Unclear risk	Not mentioned
Blinding (detection bias) - outcome assessor All outcomes	High risk	Allocation of treatments was revealed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reports results on 33 children 4 lost in the trial and results not included in either group.
Selective reporting (reporting bias)	High risk	Intention-to-treat analysis not done
Other bias	Low risk	Adverse effects mentioned

Forsythe 1972

Methods	RCT (double-blind placebo controlled, stratified by sex) Systematic baseline measure of wetting: No Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: Belfast Hospital for Sick Children
Participants	No. of children (boys): 241 (140) Dropouts before start of study: A: 10, B: 16 Dropouts before end of FU: A: 6, B: 9 Incl: nocturnal enuresis at least 6x/week in previous year Ages: 5-14 years
Interventions	A (121): Chlordiazepoxide (5 mg) + amitriptyline (12.5 mg) B (120): Placebo Duration of treatment: 8 weeks Follow up: 8 weeks
Outcomes	No. not achieving 14 dry nights: A: 109/111, B: 104/104 No. improving by 50%: A: 50/111, B: 88/104

Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) (Review)

Forsythe 1972 (Continued)

No. not achieving 14 dry nights or relapsing after: A: 103/104, B: 95/96
Improved (at least 50% dry nights): A: 69/104, B: 82/96

Notes	Chlordiazepoxide used to suppress emotional stimuli Groups and dropouts comparable	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children were allotted at random to one of the treatment groups
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Double-blind possibly patients and personnel
Blinding (performance bias) - care givers All outcomes	Unclear risk	Double-blind possibly patients and personnel
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention to treatment unclear
Selective reporting (reporting bias)	Unclear risk	Not mentioned
Other bias	Low risk	Large sample, all outcomes reported

Gelotte 2009

Methods	RCT (double-blind, placebo-controlled) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Setting: primary care practices	
Participants	Number of subjects (boys) 318 (224) Number of dropouts 22 Inclusion criteria: primary nocturnal enuresis with a minimum of 8 wet nights during the 14-day baseline period; plus many others Exclusion criteria: 12 in all Ages 6-11 years Baseline wetting: reported in table 2: 12 night/ fortnight	

Gelotte 2009 (Continued)

Interventions	A (82) ibuprofen + pseudoephedrine B (78) ibuprofen C (76) pseudoephedrine D (82) placebo Duration of treatment: 14 days Duration of follow up: none	
Outcomes	Mean wet nights during trial (ie at end of treatment) approx. 9/14 Adverse events (numbers and details) as in table 4: 20%	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization code.
Allocation concealment (selection bias)	Low risk	Each child was sequentially assigned medication (i.e. numbered boxes with attached opaque sealed envelopes containing the treatment assignment)
Blinding (performance bias) - participants All outcomes	Low risk	Participants blinded (placebo used)
Blinding (performance bias) - care givers All outcomes	Low risk	Care givers blinded
Blinding (detection bias) - outcome assessor All outcomes	Low risk	Code broken after data analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions were uniformly distributed and unrelated to medications. the over-all exclusion number was small
Selective reporting (reporting bias)	High risk	Efficacy analyses were conducted primarily using the per-protocol population, rather than the intention to treat population, since this was an exploratory study.
Other bias	Low risk	adverse events reported

Gjessing 1968#

Methods	RCT (crossover trial) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned	
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Gjessing 1968# (Continued)

Participants	Number of children (boys): 69 (37) Dropouts: 24 Incl: age 4+; no organic causes Previous treatment: none Age: 70% between 4 and 7 years Baseline wetting: wet bed at least 4 x/week for those under 7 and 2x/week for those over 7
Interventions	A (45): Chlorprotixine (Truxal) 5mg B (45): Placebo Duration of treatment: 6 weeks each arm of trial Follow up: none
Outcomes	Number of children achieving 100% dry nights: A: 4/45, B: 2/45 Side effects: drowsiness
Notes	Danish language (translated) Results not clear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Cross-over trial
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias) - participants All outcomes	Unclear risk	Placebo used therefore blinding of participants likely
Blinding (performance bias) - care givers All outcomes	Unclear risk	Not stated
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow up
Selective reporting (reporting bias)	Unclear risk	No translation available
Other bias	Unclear risk	translation of side effects NA

GP Research Gp 1970#

Methods	RCT (double-blind crossover trial) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes
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Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) (Review)

GP Research Gp 1970# (Continued)

Daytime wetting excluded: Not mentioned
Setting: community patients in 16 GP practices

Participants	No. of children (boys): 55 (33) Incl: at least 3 wet nights per week Excl: renal abnormalities Age: 5-15 years Baseline wetting: 5.6 wet nights per week (A: 5.3, B: 5.6)
Interventions	A (28): triclofos 0.5 gm B (27): ephedrine 15 mg Dose depended on age: 5-8 years = 1 tablet; 9-12 = 2 tablets; 13-15 = 3 tablets Duration of treatment: 4 weeks each arm, then crossed over Follow up: none possible
Outcomes	Mean wet nights in 4th week: A: 4.1, B: 4.5 No. not achieving 14 dry nights: A: 25/28, B: 27/28 Both arms better than baseline (by 1 wet night per week) but not different from each other
Notes	Data from first arm of trial used No SDs Triclofos is a sedative, ephedrine is a stimulant No washout

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Double-blind crossover trial
Blinding (performance bias) - care givers All outcomes	Unclear risk	Double-blind crossover trial
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Double-blind crossover trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Only wet nights per week measured as an outcome
Other bias	Unclear risk	Side effects not mentioned

Harrington 1960#

Methods	RCT (crossover trial) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: No (1 had daytime wetting)
Participants	Number of children (boys): 11 (8) Dropout: 1 Excl: ascertainable organic disease Previous treatment: 1 resection of bladder neck Age range 5 to 16 years (and one adult aged 31 years) Baseline wetting: mean number of wet nights per month A:26.7, B:22.0
Interventions	A (10): phenmetrazine (Preludin) 25mg (half tablet for young children; 2 tablets for adults) B (10): placebo Duration of treatment: 1 month each arm of the trial Follow up: none
Outcomes	Mean (SD) number of wet nights per month: Period 1 A:7.3(7.06), B:11.0(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)
Notes	Very small sample Groups do not look comparable Dropout not included in analysis Includes one adult No fluid restrictions, diet change or lifting. No follow up No washout and clear carryover effect period 1 to 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The patients were numbered and divided into two groups by random selection
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias) - participants All outcomes	Low risk	It is stated that "neither the patients nor I knew which (treatment) was which"
Blinding (performance bias) - care givers All outcomes	Low risk	It is stated that "neither the patients nor I knew which (treatment) was which"
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	One abandoned treatment early in the trial and has been excluded from the analysis.
Selective reporting (reporting bias)	Unclear risk	Unclear

Harrington 1960# (Continued)

Other bias	Low risk	All side effects reported
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Ingle 1968

Methods	CCT (alternate allocation to groups) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned
Participants	No. of children: 25 (boys A:6, B:5) Incl: wetting consistently over 3yrs Most had previous treatment from other practitioner without any relief Mean age A:8.9yrs, B:8yrs Baseline wetting: mean frequency of wetting A:8.8, B:9
Interventions	A (13): tranquillisers - meprobamate (400mg daily and hydroxyzine 1mg kg daily) B (12): imipramine 25mg daily increased to 50mg in some cases Duration of treatment: 6 weeks Follow up: 1 week
Outcomes	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
Notes	No details of blinding No details of dropouts Age, sex distribution and frequency of bed wetting comparable in groups Very short follow up No statistical analysis No details how progress monitored or when measurements taken

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternate allocation
Allocation concealment (selection bias)	Unclear risk	Not stated but could be high risk given the alternate allocation by caregivers.
Blinding (performance bias) - participants All outcomes	Unclear risk	Not stated
Blinding (performance bias) - care givers All outcomes	Unclear risk	Not stated
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not stated

Ingle 1968 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	all data accounted for
Selective reporting (reporting bias)	Low risk	all data accounted for
Other bias	Low risk	side effects reported

Kennedy 1968

Methods	CCT (alternate allocation) Systematic baseline measure of wetting: No Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: A+B clinic attenders and paediatric referrals; C+D residents in Sunland Training Centre, Florida
Participants	No. of children (boys): A+B 10 (8); C+D 8 Incl: C+D had learning difficulties Excl: organic cause for enuresis Age: A+B 6-12 years; C+D 9-12 years
Interventions	A (5): Alarm + methedrine 5mg B (5): Alarm only C (3): Alarm + methedrine 5mg D (5): Alarm only Duration of treatment: 8 weeks Follow up: 13 months
Outcomes	No. not achieving 14 dry nights: A: 0/5, B: 0/5, C: 0/3, D: 4/5
Notes	Groups A+C and B+D combined for analysis Baseline comparability not mentioned Drug did not affect outcome but numbers too small to be reliable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	alternate patients were allocated to 2 arms
Allocation concealment (selection bias)	Unclear risk	no mention of allocation concealment
Blinding (performance bias) - participants All outcomes	Unclear risk	not mentioned
Blinding (performance bias) - care givers All outcomes	Unclear risk	not mentioned
Blinding (detection bias) - outcome assessor	Unclear risk	not mentioned

Kennedy 1968 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	no loss to follow-up
Selective reporting (reporting bias)	High risk	only wet nights per week measured as outcome
Other bias	High risk	no adverse events reported

Khosroshahi 1989

Methods	RCT Systematic baseline measure of wetting: No Organic causes excluded: Yes Daytime wetting excluded: Yes Setting: Outpatient Department, Ankara
Participants	No. of children (boys): 73 (42) Dropouts: 27 other children, dropped out as uncooperative or did not attend for follow up Incl: nocturnal enuresis Excl: diurnal enuresis, encopresis, UTI, organic defects Ages: range 6-14 years (mean boys 8.5, girls 8.4)
Interventions	A (18): piracetam (20mg/kg at bedtime, maximum 800 mg) B (15): play and supportive therapy C (12): both D (14): placebo (single dose at bedtime) [E (14): non-enuretic epileptics treated with diphenylhydantoin 5mg/kg per day] Duration of treatment: 8 weeks Follow up: none
Outcomes	No. not achieving 14 dry nights during trial: A: 16/18, B: 8/15, C: 4/12, D: 9/14 Side effects: A: mild headache or nausea, number not specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned" but not clear how
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	High risk	Psychotherapy and drug combination are two therapies delivered with obvious difference thus making blinding difficult
Blinding (performance bias) - care givers All outcomes	High risk	Psychotherapy and drug combination are two therapies delivered with obvious difference thus making blinding difficult

Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) (Review)

Khosroshahi 1989 (Continued)

Blinding (detection bias) - outcome assessor All outcomes	High risk	Psychotherapy and drug combination are two therapies delivered with obvious difference thus making blinding difficult
Incomplete outcome data (attrition bias) All outcomes	High risk	100 included but 73 reported
Selective reporting (reporting bias)	Low risk	single outcome of interest to this review
Other bias	Unclear risk	adverse effects ?

Kline 1968

Methods	RCT Systematic baseline measure of wetting: No Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: Department of Paediatrics, Baylor
Participants	No. of children: 50 Incl: nocturnal enuresis Excl: organic uropathy, mental retardation Ages 3-15 years
Interventions	A (28): diazepam 15 mg per day increased to 25 mg if no response B (22): matching placebo Duration of treatment: 4 weeks. If poor response then given open label diazepam for 8 weeks, if good response continued on A or B as allocated, therefore follow up not possible
Outcomes	Mean wet nights per week in 4th week: A: 1.04 (SD 2.53), B: 5.91 (2.43) No. not achieving 14 dry nights during trial: A: 6/28, B: 21/22 Adverse events causing discontinuation: A: 1 (drowsiness, ataxia), B: 1 (insomnia and hyperactivity)
Notes	Results from first 4 weeks only Baseline comparability of groups not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not mentioned; may not be done
Allocation concealment (selection bias)	Unclear risk	not enough information to permit judgement
Blinding (performance bias) - participants All outcomes	Low risk	clearly mentioned that the drug was unidentifiable
Blinding (performance bias) - care givers All outcomes	High risk	Caregiver cannot be blinded if increasing dose of treatment

Kline 1968 (Continued)

Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	no loss to follow-up
Selective reporting (reporting bias)	Low risk	single outcome well reported
Other bias	Low risk	adverse effects reported

Korczyn 1979#

Methods	Design: double-blind crossover Systematic baseline measure of wetting wet at least 3 nights per week Organic causes excluded YES Daytime wetting specifically excluded? Not mentioned Setting/recruitment: Not mentioned
Participants	Number of subjects (boys) 20 (unknown) Number of dropouts 6 Inclusion criteria: wetting 3 or more times per week Exclusion criteria: neurological abnormality, obvious psychological difficulties Ages: 5-15 years Baseline wetting: not mentioned
Interventions	A (14) imipramine B (14) scopolamine butylbromide (does not cross blood brain barrier) 10mg C (14) placebo D (7) double dose scopolamine butylbromide 20mg Duration of treatment: 1 month for some, 3 weeks for some Duration of follow up: length of treatment
Outcomes	Wet nights on treatment = Mean wet nights per month at end of treatment: A:10.57 ± 5.42, B:14.86 ± 6.98, C:15.64 ± 7.7 D: 15.43 ± 12.31
Notes	Unequal treatment periods
Risk of bias	
Bias	Authors' judgement Support for judgement

Korczyn 1979# (Continued)

Random sequence generation (selection bias)	Unclear risk	not mentioned
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias) - participants All outcomes	Unclear risk	double blind but not sure who was blinded
Blinding (performance bias) - care givers All outcomes	Unclear risk	double blind but no details
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	6 drop outs out of 20
Selective reporting (reporting bias)	High risk	no intention to treat analysis
Other bias	High risk	unequal treatment periods, no washout

Kunin 1970#

Methods	RCT (double-blind randomised crossover with 1 week washout) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes
Participants	No. of children (boys): 18 (8) Incl: average of 3 wet nights per week; no diurnal wetting Previous treatment: no details Mean age 7.7 years (range 5-11) Severity at baseline: mean number of wet nights over 28 days: 19.8
Interventions	A (18): imipramine hydrochloride (25 or 50mg) B (18): ephedrine sulphate (7.5 or 15mg) Duration of treatment: 28 days in each condition Follow up: not specified
Outcomes	Mean number (SD) of wet nights over 28 days: A:9.2 (6.72), B:17.4 (5.8) 5 children became completely dry but all required medication. Eight children were dry >90% of the time with 2 children needing no further medication
Notes	Unclear if intention to treat Only part of trial (children with no organic causes) included here

Risk of bias

Bias	Authors' judgement	Support for judgement
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Kunin 1970# (Continued)

Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Low risk	Patients received a coded medication assigned according to a randomised list by an administration officer who was not part of the trial
Blinding (performance bias) - participants All outcomes	Unclear risk	Insufficient information
Blinding (performance bias) - care givers All outcomes	Unclear risk	Insufficient information
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention to treat unclear
Selective reporting (reporting bias)	Unclear risk	Intention to treat unclear
Other bias	Unclear risk	Adverse effects?

Lee 2005

Methods	Design: RCT Systematic baseline measure of wetting YES Organic causes excluded YES Daytime wetting specifically excluded? NO Setting/recruitment: clinics at 2 hospital
Participants	158 but 13 data missing; 145 (100) participants Inclusion criteria: documented history of PNE with minimum 3 wet nights/wk, no use of drugs that could affect NE for 14 days before study entry Exclusion Criteria: UTI or other organic urological disease Ages: 6-15 Baseline wetting: A=13.3 +/-3.4, 12.0 +/- 3.5, 13.2 +/-2.9
Interventions	A (51/48) combination desmopressin (0.1-0.2mg) + oxybutynin (5mg) B (52//49) desmopressin (0.2-0.4mg) C (55/48) imipramine (25mg) Duration of treatment: 6 months

Lee 2005 (Continued)

Duration of follow up: 6 months

Outcomes

wet nights on treatment = Mean wet nights at end of treatment (at 6 months)

A = 3.7 +/- 5.4 per 14 nights, B = 4.0 +/- 4.6, C = 9.3 +/- 8.3

2. # not achieving 14 consecutive dry nights - fail = # not achieving 14 dry nights at end of treatment = 6 months ("excellent" assumed to mean 14 consecutive dry nights)

A = (51-23) = 28; B = (52 - 21) = 31; C = (55 - 6) = 49

(Dry: A = 47.9% = 23, B = 42.9% = 21, C = 12.5% = 6)

Adverse events (numbers and details):

Severe headaches in 2 patients in desmopressin group, nausea, decreased appetite, mood changes in 22 patients in imipramine group.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias) - participants All outcomes	Unclear risk	Not specified
Blinding (performance bias) - care givers All outcomes	Unclear risk	Not specified
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	participants who did not complete 6 months of treatment excluded from the analysis
Selective reporting (reporting bias)	High risk	participants who did not complete 6 months of treatment excluded from the analysis
Other bias	High risk	varying doses of drugs, dose titrated for each patient depending on response

Leys 1956

Methods

CCT (double-blind to children and staff but alternate allocation to groups)

Systematic baseline measure of wetting: Yes

Organic causes excluded: No

Daytime wetting excluded: Not mentioned

Leys 1956 (Continued)

Setting: 29 'disturbed boys' from childrens' homes, rest at home in the community

Participants	No. of children: 65 reported Dropouts: A: 8, B: 9 before start of trial Incl: at least 2 wet nights/ 2 weeks, age range 5-15 Baseline wetting: A: mean 5.21/week, B: 4.94
Interventions	A (33): propantheline bromide 15 mg for 4 days, then 30 mg for 4 days, then 45 mg for 6 days B (32): placebo Duration of treatment: 2 weeks Follow up: 4 weeks
Outcomes	Mean wet nights per week during trial: A: 4.7, B: 5.36 (difference stated to be significant, $P < 0.01$) No. of children cured: none Mean wet nights per week after trial: A: 4.96, B: 5.33
Notes	No SDs Propantheline has an antiparasymphathetic (anticholinergic) action Groups comparable at baseline on age

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	None attempted
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Low risk	Blinding meticulously observed
Blinding (performance bias) - care givers All outcomes	Low risk	Blinding meticulously observed
Blinding (detection bias) - outcome assessor All outcomes	Low risk	Blinding meticulously observed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up even during follow-ups.
Selective reporting (reporting bias)	Low risk	No loss to follow-up even during follow-ups.
Other bias	High risk	Adverse effects not mentioned

Marconi 1985

Methods	RCT (no details) Systematic baseline measure of wetting: No Organic causes excluded: Yes
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Marconi 1985 (Continued)

Daytime wetting excluded: Not mentioned
Setting: paediatric urology clinic, Varese, Italy

Participants	Number of children: 58 Dropouts: 0 Incl: severe enuresis (7 wet nights per week) Excl: organic causes, other illnesses, UTI Previous treatment: not stated Ages: 5-14 years
Interventions	A (29): oxybutynin (5mg 3 times a day) B (29): dicyclomine (20mg 3 times a day) Duration of treatment: 4 weeks Follow up: none (responders continued on the drug, non-responders received the alternative)
Outcomes	Wet nights in 4th week: A: 1.1 (SD 1.7), B: 6.8 (0.5) Responders (reduction of 40% in wet nights): A: 26/29, B: 4/29 Side effects: on oxybutynin during trial or afterwards: visual disturbances 29.6%, xerostomia 55.5%, digestive disturbances 18.4%, nausea 16.6%, vertigo 9.2%, tachycardia 7.4%, tachycardia 20%, headache 7.4%. None were serious enough to discontinue treatment
Notes	Data estimated from graph

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	randomised into 2 groups however method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias) - participants All outcomes	Unclear risk	Only one arm crosses over therefore not sure who was blinded
Blinding (performance bias) - care givers All outcomes	Unclear risk	Only one arm crosses over therefore not sure who was blinded
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Only one arm crosses over therefore not sure who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No loss to follow-up.
Selective reporting (reporting bias)	High risk	as above
Other bias	Low risk	adverse effects stated

Mayon-White 1956

Methods	CCT (alternate allocation by last digit of hospital number) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: children's outpatient clinic, Ipswich and East Suffolk
Participants	Number of children (boys): 15 (12) Incl: consecutive children referred with enuresis Excl: organic causes Previous treatment : 4 Ages 3-15 years (mean A: 6.2, B: 9.4), but only 3 children under 6 years Baseline wetting: more than half the nights were wet
Interventions	A (9): propantheline 30 mg (1 tablet for 4 weeks, 2 tablets for 4 weeks then crossed over to B B (6): placebo (matching regime) Duration of treatment: 12 weeks Follow up: not possible
Outcomes	Mean wet nights during trial: A: 2.11, B: 1.75 No. not achieving 14 dry nights: A: 2/9, B: 1/6 Side effects: A: 2 (dry mouth), B: 1 (dry mouth)
Notes	No SDs Data from parallel group arms All children also received routine management including avoidance of blame, rewards for dry nights and fluid restriction Control group older and had more wet nights at baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	randomisation based on hospital record numbers
Allocation concealment (selection bias)	Low risk	Hospital pharmacist dispensed tablets active or blank
Blinding (performance bias) - participants All outcomes	Low risk	hospital pharmacist dispensed medication based on randomisation, tablets were identical in appearance
Blinding (performance bias) - care givers All outcomes	Unclear risk	hospital pharmacist dispensed medication based on randomisation, tablets were identical in appearance
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	hospital pharmacist dispensed medication based on randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	single outcome well reported
Other bias	Unclear risk	adverse effects?

Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) (Review)

Moltke 1979

Methods	RCT (double-blind) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned
Participants	No. of children 88 (boys 62%) Dropouts: 47 Previous treatment: no details Age range: 4-13 years Average age: 8 years Severity of wetting at baseline: mean percentage of bed wetting frequency A:77%, B:81%, C:79%
Interventions	A (41): furosemide (Lasix) 40mg B (43): imipramine 25mg C (44): placebo Doses increased if no response Duration of treatment: 4 weeks Follow up: 1 year
Outcomes	At end of study mean percentage wet nights per week: A: 73%, B: 49%, C: 67% When followed up after 1 year, 59 children had increased frequency of wetting to baseline level or worse
Notes	Danish paper No SDs No details of reasons for dropouts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias) - participants All outcomes	Unclear risk	Double blind but not mentioned who is blinded
Blinding (performance bias) - care givers All outcomes	Unclear risk	Double blind but not mentioned who is blinded
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Assessors blinding not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	all outcomes reported

Moltke 1979 (Continued)

Other bias	Low risk	adverse effects reported
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Natochin 2000

Methods	CCT (randomisation using case record numbers) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Setting: St Petersburg State Medical Academy, Russia
Participants	No. of children: 62 (43 boys) plus 22 (15) on placebo Incl: primary nocturnal enuresis Excl: other medication, daytime wetting, other disease Age range 6-15 years (mean 9.8 +/- 7) Baseline wetting at least 6 wet nights per 2 weeks
Interventions	A (32): desmopressin 10.5 - 24.5 µg intranasally B (30): diclofenac tablet 1 mg/kg body mass C (22): Placebo (intranasally) for 2 weeks then given desmopressin Duration of treatment: A and B 4 weeks each, C (placebo) 2 weeks only Follow up: none
Outcomes	No. not achieving 14 dry nights: A: 11/32; B: 20/30; C: 21/22 Side effects: none reported
Notes	Extra information supplied by authors (method of randomisation, results confirmed, no side effects) Parallel groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Used case record numbers
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias) - participants All outcomes	High risk	not possible since open label
Blinding (performance bias) - care givers All outcomes	High risk	not possible since open label
Blinding (detection bias) - outcome assessor All outcomes	High risk	not possible since open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.

Natochin 2000 (Continued)

Selective reporting (re-reporting bias)	Low risk	No selective reporting of outcomes
Other bias	Low risk	side effects reported

Neveus 2008#

Methods	Design: Randomised crossover design Systematic baseline measure of wetting YES Organic causes excluded YES Daytime wetting specifically excluded? NO, previous daytime wetting ok Setting/recruitment unclear, possibly hospital clinics since author is a nephrologist
Participants	Number of subjects (boys): 27 (22) Number of dropouts: 2 (1 dry, 1 side effects) Inclusion criteria: wet at least 7/14 nights, failed alarm therapy and desmopressin monotherapy Exclusion criteria: Daytime wetting, concomitant cardiac, nephrologic, metabolic or neuro-urolgic disease, urinary tract infection or previous treatment with anticholinergic or tricyclic drugs Ages: 6-13, mean 9.4 ± 2.1 Baseline wetting: 11.0 ± 3.6 per 14 nights
Interventions	A (25) placebo B (25) tolterodine C (25) imipramine Duration of treatment: 5 weeks Duration of follow up: (measured only last 2 weeks of treatment)
Outcomes	Mean wet nights during trial (ie at end of treatment) A 11.9 ± 3.9 out of 14 B 10.4 ± 3.9 C 7.8 ± 5.1 No. not achieving 14 dry nights during trial (ie at end of treatment) A (assumed) (25/25), B=25/25, C=20/25 No. not achieving 14 dry nights during trial or relapsing after (ie at follow up) At end of trial, children received various treatments, therefore follow up not meaningful Mean wet nights after end of trial (ie at follow up) As above Adverse events (numbers and details)

Neveus 2008# (Continued)

9 from imipramine and 1 from tolterodine

Nine patients experienced side effects during imipramine treatment (three slight mood change, two insomnia, one palpitations, two slight nausea and one child interrupted medication because of intense nausea), whereas one had side effects (slight mood change) during the tolterodine period and none during placebo treatment.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation strategy not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Mentioned to be double-blind
Blinding (performance bias) - care givers All outcomes	Unclear risk	Mentioned to be double-blind
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Outcome assessor blinding not considered or mentioned; probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Addressed clearly. One child became spontaneously dry during the first treatment period (placebo, in her case) and has remained dry ever since. Another patient dropped out due to side effects, but no one dropped out due to protocol failure. This left us with 25 patients for the final analysis. Nine patients experienced side effects during imipramine treatment (three slight mood change, two insomnia, one palpitations, two slight nausea and one child interrupted medication because of intense nausea), whereas one had side effects (slight mood change) during the tolterodine period and none during placebo treatment. The different proportions of side effects between the treatments was statistically significant (Cochran Q test, $P=0.001$)
Selective reporting (reporting bias)	High risk	Intention-to-treat analysis not performed
Other bias	Low risk	All outcomes reported

Petersen 1974#

Methods	RCT (randomised double-blind crossover) Systematic baseline measure of wetting: No Organic causes excluded: No Daytime wetting excluded: No Setting: Outpatient clinic
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Petersen 1974# (Continued)

Participants	No. of children: 69 Dropouts: 7 Incl: primary and secondary enuresis, some diurnal wetting, organic causes or behavioural disturbances Excl: none Previous treatment: almost all (waking, alarms, drugs, hospital admission) Ages: 5-15 years (mean for boys 8 years 6 months, girls 8 years 3 months)
Interventions	A (61): imipramine B (61): imipramine-N-oxide C (61): emepronium (Cetiprin) D (61): placebo (all matching preparations) Duration of treatment: 4 weeks on each drug Follow up: children continued on one successful drug for 3 months: A: 32 children, B: 10, C: 2, D: 4
Outcomes	Mean wet nights per week in last 3 weeks of each drug: A: 2.4, B: 3.24, C: 4.36, D: 4.37 Adverse events: A: 13, B: 7, C: 10, D: 11 (nausea, decreased appetite, sleep disturbance, rash, headaches, sweating, fatigue, sullenness, tremor)
Notes	No SDs No washouts All children had fluid restriction and waking once a night

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The preparations were administered together in a randomised order
Allocation concealment (selection bias)	Unclear risk	Using a double-blind technique but method not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Double-blind, probably the patients and personnel
Blinding (performance bias) - care givers All outcomes	Unclear risk	Double-blind, probably the patients and personnel
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Salmon 1973#

Methods	RCT (double-blind crossover trial) Systematic baseline measure of wetting: No Organic causes excluded: No Daytime wetting excluded: Not mentioned Setting: hospital enuresis clinic
Participants	No. of children: Trial 1: 53, Trial 2: 24 Incl: consecutive children with primary nocturnal enuresis, age over 5.5 years
Interventions	Trial 1 A (53): oxazepam ('Serenid') 10 mg 2x or 3x/day B (53): placebo Trial 2 C (24): chlorthalidone ('Librium') 10 mg 3x/day D (23): placebo Duration of treatment, trial 1: 2 months each arm
Outcomes	Trial 1: 'an increase in dry nights with A only slightly greater than with Placebo B' Trial 2: C 'during the day gave a statistically significant improvement ($P<0.001$) compared with placebo D'
Notes	No useable data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used a randomised chart for the order of treatment
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Double-blind study, possibly patients
Blinding (performance bias) - care givers All outcomes	Unclear risk	Double-blind study, possibly physician
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned, probably not done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Single outcome reported and loss to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	Single outcome reported and loss to follow-up not reported
Other bias	Unclear risk	Adverse effects not reported

Sener 1998

Methods	RCT (method not specified) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned
Participants	No. of children: 85 Incl: primary enuresis, age >5yr Excl: enuresis treatment, other disease symptoms Age range 6-15, mean 8 years Baseline wetting at least 3 wet nights/week Dry nights in 2 weeks: A: 1.5 (SE 0.3); B: 1.5 (0.4); C: 1.1 (0.3)
Interventions	A (31): desmopressin 20 mcg, intranasally B (29): indomethacin 100 mg/day, suppository C (25): placebo Duration of treatment: 4 weeks Follow up: none
Outcomes	Mean DRY nights/2 weeks (SE) on treatment: A: 31, 11.8 (0.5); B: 29, 8.9 (0.8); C: 25, 3.8 (0.8) [= wet nights per week: A: 31, 1.1 (SD 1.39); B: 29, 2.55 (2.15); C: 25, 5.1 (2)] Side effects: none reported
Notes	Parallel groups Blinding not possible due to different routes of administration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not mentioned
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias) - participants All outcomes	High risk	Blinding not possible due to different routes of administration
Blinding (performance bias) - care givers All outcomes	High risk	Blinding not possible due to different routes of administration
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	loss to follow-up not mentioned
Selective reporting (reporting bias)	Unclear risk	loss to follow-up not mentioned and hence difficult to say
Other bias	Unclear risk	side effects not reported

Shaffer 1978#

Methods	RCT (double-blind crossover trial) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: referrals from local authority enuresis clinic to Dept Psychiatry, New York
Participants	No. of children (boys): 14 (6) Dropouts: 8 (4 not wet enough, 4 other reasons) Incl: school age, wet at least 8 nights /2 weeks Ages: mean 8 years, 3 months, range 4,7 to 12,2
Interventions	A (14): Indoramin 20 mg B (14): Indoramin 10 mg C (14): placebo Duration of treatment: 2 weeks in each arm
Outcomes	Mean DRY nights in 2 weeks: A: 3.61, B: 4.03, C: 3.3 'no significant differences or order effects' Trialists' conclusion: alpha blockade does not improve enuresis
Notes	Indoramin = alpha-adrenoceptor blocker No washout phase No SDs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were allocated at random into treatment groups
Allocation concealment (selection bias)	Unclear risk	Treatment varied in content according to a predetermined schedule
Blinding (performance bias) - participants All outcomes	Unclear risk	Not mentioned
Blinding (performance bias) - care givers All outcomes	Low risk	The outcome was not known to any of the clinic staff seeing the child
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 14 patients were included in the analysis
Selective reporting (reporting bias)	High risk	Originally 22 patients agreed to participate but 8 dropped out before treatment allocation
Other bias	High risk	No washout

Sumner 2006

Methods	RCT (double-blind, parallel group, placebo controlled randomised trial) Method of allocation or concealment not described Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: No Setting: outpatient trial in more than one centre
Participants	No. of children (boys): 87 (64) Dropouts: A: 9/44, B: 9/43 Incl: nocturnal enuresis, washout period after excluded medications Ages (mean years): A: 10.22 (SD 2.02), B: 9.12 (1.89) P=0.011, Group A children significantly older than Group B Baseline wetting (mean dry nights per week): A: 1.51, B: 1.01 (A significantly more dry nights)
Interventions	A (44): atomoxetine, increasing dose over first 3 days until 1.5 mg/kg in 2 divided doses B (43): matching placebo Duration of treatment: 12 weeks Follow up: none
Outcomes	Dry nights per week (mean): A: 2.98, B: 1.61 (P= 0.010) Number of children with no wet nights in last week of treatment: A: 8/42, B: 0/41 Adverse effects causing discontinuation: A: 2/44, B: 1/43 Weight change: A: 0.45 kg loss, B: 1.08 gain Increased pulse rate to over 20 beats per minute: A: 6/44, B: 0/43
Notes	Research funded by drug company Groups not comparable at baseline on number of dry nights (A better), age (A older), number of children with attention-deficit /hyperactivity disorder (A fewer) No SDs Atomoxetine is an inhibitor of the presynaptic norepinephrine transporter, i.e. it has an adrenergic agonist effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised double-blind placebo controlled study. Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated
Blinding (performance bias) - participants All outcomes	Unclear risk	Double-blind study, doesn't mention who was blinded
Blinding (performance bias) - care givers All outcomes	Unclear risk	Double-blind study, doesn't mention who was blinded
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Double-blind study, doesn't mention who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	This study used an Intent-To-Treat (ITT) analysis that requires that data be used from all patients who were randomized to a treatment, even if a patient does not complete the

Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) (Review)

Sumner 2006 (Continued)

		study.
Selective reporting (reporting bias)	Low risk	Detailed outcome reporting
Other bias	Low risk	Side effects reported

Tahmaz 2000

Methods	RCT (divided at random into 4 groups) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Setting: Dept Urology, Military Medical Faculty, Turkey
Participants	No. of children (boys): 77 (48) Dropouts: A: 2, B: 7, C: 2, D: 9 (not explained) Incl: primary nocturnal enuresis, ≥ 3 wet nights/week, no current treatment Excl: organic causes, daytime wetting, UTI Ages: 6-14 years (9.44 +/- 2.17)
Interventions	A (14): imipramine 0.9-1.5 mg/kg/day B (16): oxybutynin 5 mg 3x/day C (24): imipramine + oxybutynin D (23): placebo (not described) If cured, treatment tapered off gradually Duration of treatment: 3 months Follow up: 6 months
Outcomes	Cure defined as $>90\%$ reduction in wet nights Failed: A: 7/14, B: 10/16, C: 8/24, D: 18/23 Failed or relapsed: A: 10/12, B: 8/9, C: 10/22, D: 11/14 Side effects: A: 3/14 (dry mouth, nausea), B: 4/16 (dry mouth, nausea), C: 7/24, D: 4/23
Notes	Groups comparable at baseline on age, sex and disease severity but groups of unequal sizes No details of previous treatment No details of nature of placebo treatment Cure not defined as complete dryness

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were divided at random into 4 groups. Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated
Blinding (performance bias) - participants All outcomes	Unclear risk	This study was designed on a single-blind basis
Blinding (performance bias) - care givers All outcomes	Unclear risk	Not mentioned

Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics) (Review)

Tahmaz 2000 (Continued)

Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Results have been recorded for all 77 patients
Selective reporting (reporting bias)	Unclear risk	Not mentioned
Other bias	High risk	few details

Van Hoeck 2008

Methods	Design RCT Systematic baseline measure of wetting NO Organic causes excluded YES Daytime wetting specifically excluded? Not mentioned Setting/recruitment: Hospital based
Participants	Number of subjects (boys): 149 (108) Number of dropouts: 20 Inclusion criteria 14 WET nights in 4 weeks Exclusion criteria functional and anatomic incontinence Ages median 7.5 (5.9-12.7) years Baseline wetting not given
Interventions	A (29) holding exercises plus placebo (12 weeks) f/b alarm (12 weeks) B (30) holding exercises plus oxybutynin (12 weeks) f/b alarm (12 weeks) C (30) placebo only (12 weeks) f/b alarm (12 weeks) D (30) oxybutynin only (12 weeks) f/b alarm (12 weeks) E (30) controls, alarm only Duration of treatment 24 weeks Duration of follow up 52 weeks
Outcomes	No. not achieving 14 dry nights during trial (ie at end of treatment) A (12/25) B (14/29) C(14/28) D (13/27) E (7/28) No. not achieving 14 dry nights during trial or relapsing after (ie at follow up) A (10/22) B (14/28) C(9/26) D (13/26) E (11/27)
Notes	

Van Hoeck 2008 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation used but method not stated
Allocation concealment (selection bias)	High risk	Not possible due to the nature of interventions used
Blinding (performance bias) - participants All outcomes	High risk	Not possible due to the nature of interventions used
Blinding (performance bias) - care givers All outcomes	High risk	Not possible due to the nature of interventions used
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	incomplete data small and accounted for
Selective reporting (reporting bias)	Low risk	ITT analysis used
Other bias	Unclear risk	adverse events not mentioned

Varan 1996

Methods	RCT Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: Dept Paediatric Nephrology, Turkey
Participants	No. of children: 29 Incl: primary nocturnal enuresis for 6 months, age over 5 years, at least 3 wet nights in last 2 weeks Excl: neurological or renal disease, dry period for more than 6 months Ages: 6-15 years (mean A: 10.8, B: 8.6, C: 9) Baseline dry nights in 2 weeks: A: 2.4 (SD 2.2), B: 2.5 (2.2), C: 2 (2.3)
Interventions	A (9): oxybutynin 0.5 mg/kg B (11): pseudoephedrine 2 mg/kg C (9): indomethacin 2 mg/kg Duration of treatment: 4 weeks Follow up: none
Outcomes	Mean DRY nights in 2 weeks: A: 4.7 (SD 3.9), B: 6.2 (3.8), C: 4.3 (4) [= wet nights per week: A: 9, 4.65 (SD 1.95); B: 11, 3.9 (1.9); C: 9, 4.85 (2)] Adverse events: A: 3 epistaxis, 1 flushing, 1 voiding difficulty, B: none, C: 1 gastrointestinal irritation

Varan 1996 (Continued)

Notes Groups comparable at baseline on age, urinalysis, dry nights, family history, socioeconomic conditions, but group A older

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children were randomly put on treatment
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	Unclear risk	Not mentioned
Blinding (performance bias) - care givers All outcomes	Unclear risk	Not mentioned
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Not mentioned
Other bias	Low risk	Adverse events reported

Wallace 1969

Methods	RCT Systematic baseline measure of wetting: No Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: Belfast hospital
Participants	No. of children (boys): 300 (167) Dropouts: 67 (A: 22, B: 28, C: 17) Incl: ages 4-14 years, wet at least 6x/week for at least 1 year Ages: 4 years 11 months to 14 years
Interventions	A (78): propantheline (3 x 15mg) B (72): propantheline (3 x 15mg) + phenobarbitone (15mg) C (83): placebo (3 x) Duration of treatment: 4 months (reducing dose by 1 tablet a week in last 2 months) Follow up: none
Outcomes	No. cured: A: 7/78, B: 10/72, C: 6/83 No. 50% improved: A: 18/78, B: 15/72, C: 19/83

Wallace 1969 (Continued)

Toxic effects caused dropout in 12 children (A: 4 headache, dry mouth, B: 8 headache, dry mouth, skin rash, C: 0 causing dropout but several had headache, abdominal pain, vertigo)

Notes Groups comparable at baseline on age, sex
Propantheline is an anti-cholinergic, phenobarbitone is a sedative

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated, tablets identical
Blinding (performance bias) - participants All outcomes	Low risk	Tablets identical
Blinding (performance bias) - care givers All outcomes	Unclear risk	Not stated
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	18% loss to follow-up; data accounted for, and well distributed across groups
Selective reporting (reporting bias)	High risk	no intention to treat analysis
Other bias	Low risk	side effects mentioned

Wright 1974

Methods RCT (medications on double-blind basis)

Systematic baseline measure of wetting: Yes
Organic causes excluded: Yes
Daytime wetting excluded: Not mentioned

Participants No. of children: 23
Dropouts: A: 0 B: 0 C: 2 D: 0

Age range 4 to 10 years
Baseline wetting: mean number of wettings per week: A + B: 4.9 C: 3.0 D: 6.6

Interventions A (3): amphetamine sulphate (2.5mg)
B (5): ephedrine sulphate (75mg) + atropine sulphate (Enuretrol, 1.15mg)
C (5): placebo twice daily
D (10): enuresis alarm

Duration of treatment: 5 weeks

Wright 1974 (Continued)

FU after 4 weeks

Outcomes	Mean number of wet nights in final week of treatment: A+B:4.1, C:3.5, D:1.7
Notes	No SDs Data estimated from graph Groups seem very different at baseline More likely to detect more wettings per night in pad and bell group All active drugs groups combined No details of inclusion\exclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentioned but not explicit
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias) - participants All outcomes	High risk	Only for drugs, not possible for the alarm group
Blinding (performance bias) - care givers All outcomes	High risk	Only for drugs, not possible for the alarm group
Blinding (detection bias) - outcome assessor All outcomes	High risk	Only for drugs, not possible for the alarm group
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data accounted for
Selective reporting (reporting bias)	Low risk	All data accounted for
Other bias	Unclear risk	Side effects not mentioned

Yukse 2003

Methods	RCT (Participants divided into two groups) Systematic baseline measure of wetting: No Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: not mentioned
Participants	No. of children (boys): 24 (10) No of dropouts: none Incl: patients scored as class 1/2 NE Excl: organic urinary tract disorders (UTI, VUR or PUV) or had taken drugs that would affect voiding / bladder function

Yuksekk 2003 (Continued)

Ages: 4-13 years (mean 7.67 years in acupressure, 7.41 in oxybutynin)

Interventions	A (12): oxybutynin 0.4 mg/kg once a day B (12): acupressure
Outcomes	Both, acupressure and oxybutynin can be used to treat NE partially, acupressure has the advantage of being non-invasive.
Notes	3 pts were assigned to acupressure because they had received unsuccessful pharmacological therapies before, suggesting that it was not truly random

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants divided into two groups
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias) - participants All outcomes	High risk	Drugs versus acupressure
Blinding (performance bias) - care givers All outcomes	High risk	Drugs versus acupressure
Blinding (detection bias) - outcome assessor All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	No baseline data
Other bias	Unclear risk	Not reported

cc = cubic centilitres; Excl = Exclusion criteria; FU = follow up; Incl = Inclusion criteria; m = month(s); NSAID = non-steroidal anti-inflammatory drug; OP = hospital outpatient department; RCT = Randomised controlled trial; SD = Standard Deviation; SEM = standard error of the mean; w = week(s); y = year(s);

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adler 1959	RCT: No Comparison group: No Organic causes excluded: No Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Equanil

Study	Reason for exclusion
Al-Waili 2000	RCT: Yes but excluded as all children had detrusor instability Comparison group: Yes Organic causes excluded: Yes Systematic baseline measurement of wetting: Yes Systematic outcome measures: Yes Intervention: carbamazepine versus placebo
Arajarvi 1977	RCT: No Comparison group: Yes Organic causes excluded: Yes Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Antidepressants
Ayan 2007	RCT: Yes but excluded as only 27/71 children had nocturnal enuresis Population: children with voiding dysfunction Intervention: Tolterodine, behavioural modification (timed voiding, double voiding and pelvic floor relaxation), placebo
Buttarazzi 1977	RCT: No Comparison group: No Organic causes excluded: Yes Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Oxybutinin
Caione 1995	RCT: Yes but participants all had daytime wetting as well as bedwetting, and some adults were included Interventions: desmopressin, oxybutynin
Cheng 2008	Vitamin B injection on acupoints versus imipramine text not available more appropriate in acupuncture related reviews
Chertin 2007	Design RCT Systematic baseline measure of wetting: yes for DVSS score but not broken down to DUI and NE Organic causes excluded YES Daytime wetting specifically excluded? NO Setting/recruitment: referred pt with ADHD and NE (? Clinic) Number of subjects (boys) 54 (34) Number of dropouts – not given Inclusion criteria: pt with ADHD and NE A (27) Desmopressin and oxybutynin B (27) Imipramine Only data available: Incidence of NE (DVSS score q2) 0.9 ± 0.2 versus 2.9 ± 0.2 $P < 0.0001$ Authors contacted by email; no response
Cortina 1994	RCT: No

Study	Reason for exclusion
	Comparison group: No Organic causes excluded: No Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Ilex paraguensis (homeopathic remedy)
Cupalova-Naglova 1970	not a RCT, academic dissertation insufficient data
De Castro 1985	RCT: No Comparison group: No Organic causes excluded: Yes Systematic baseline measurement of wetting: Yes Systematic outcome measures: Yes Interventions: Oxybutinin
Elmer 1988#	Design: double-blind modified crossover Systematic baseline measure of wetting wet at least 3 nights per week Organic causes excluded YES Daytime wetting specifically no the main focus of the study was to see the effect on overactive bladder symptoms Only one outcome relevant to this review Setting/recruitment: hospital trial focussed on overactive bladder
Festqe 1989	RCT: Yes but children had vesicoureteric reflux and detrusor instability Intervention: Propiverine
Grassetti 1986	RCT: No Comparison group: No Organic causes excluded: Yes Systematic baseline measurement of wetting: Yes Systematic outcome measures: Yes Interventions: Oxybutinin
Hellstrom 1989	RCT: Yes but children had detrusor instability and urge incontinence Intervention: Terodiline
Holt 1956	RCT: Yes (double-blind placebo controlled crossover trial) but excluded as some children allocated to more than one trial, and doses sometimes doubled, therefore no useable data Comparison group: Yes Organic causes excluded: Yes Systematic baseline measurement of wetting: No Systematic outcome measures: No Interventions: Propantheline 60mg; amphetamine sulphate; posterior pituitary snuff; and matching placebos
Ishigooka 1992	RCT: No Comparison group: No Organic causes excluded: Yes Systematic baseline measurement of wetting: Yes Systematic outcome measures: Yes

Study	Reason for exclusion
	Interventions: Terodiline
Jensen 1982#	<p>RCT (double-blind crossover trial) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: At home</p> <p>No. of children (boys): 23 (15) Incl: primary nocturnal enuresis, no fluid restriction, at least 5 wet nights/month, no current treatment Excl: urinary tract abnormalities Previous treatment: no information Ages: range 6-15 years</p> <p>A (23): cetiprin 200 mg (emepronium bromide) B (23): placebo</p> <p>Duration of treatment: 6 weeks each arm</p> <p>Follow up: none</p> <p>Results given relative to placebo arm: 2.7 more dry nights with cetiprin than placebo; and 4.3 more dry nights with cetiprin than during baseline observation (not statistically significant, data not provided). 11/23 children had more dry nights with A than B; 5/23 had the same number on A and B; and 7/23 had fewer. Adverse events: none Trialists' conclusion: cetiprin had no effect</p> <p>No useable data Danish language Groups comparable at baseline on age and sex No washout mentioned</p>
Jiang 2000	Acupuncture, not drugs
Jones 1959	<p>RCT: No Comparison group: Yes Organic causes excluded: No Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Pituitary snuff and propantheline</p>
Kajiwara 2010	<p>Design: case control (group matched for age, wetting severity and overnight urine volume)</p> <p>Systematic baseline measure of wetting YES / NO</p> <p>Organic causes excluded YES</p> <p>Daytime wetting specifically excluded? Yes (cured from previous urge incontinence)</p> <p>Setting/recruitment: outpatients department</p>
Kamel 1969	<p>RCT: No Comparison group: No Organic causes excluded: Yes Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Preludin</p>

Study	Reason for exclusion
Kapoor 1969	RCT: No Comparison group: Yes Organic causes excluded: Yes Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: methyl amphetamine (methedrine)
Kroll 2006	Not PNE
Lake 1979	The outcomes measured in this study (BP and plasma norepinephrine levels) are not related to nocturnal enuresis. This is part of larger study (reference 16, but not provided with full references)
Lee 2002	Abstract only, insufficient data, republished in 2005 as full manuscript (included)
Li 2002	Does not have drugs as a study arm
Lopez 2003	Not PNE
Lovering 1988#	RCT (crossover trial) Oxybutynin versus placebo No useable data Only a mean difference of -1.87 wet nights (? per week? per month), P=0.181
Marson 1955	METHODS – exclude as trial of “pituintrin snuff” – desmopressin (to go in desmopressin review) Design – Crossover Systematic baseline measure of wetting: YES Organic causes excluded: YES Daytime wetting specifically excluded? YES Setting/recruitment: 4 case reports
Martins 1994	Design: Randomised and double-blind Systematic baseline measure of wetting YES Organic causes excluded YES Daytime wetting specifically excluded? NO Setting/recruitment: Children with functional enuresis and depression, according DSM-III-R (table 4) Number of subjects (boys) 60 children, but the number of boys is not mentioned Inclusion criteria Functional enuresis; provide primary and secondary forms, night, night& daytime and diurnal enuresis. Exclusion Criteria Enuresis with organic causes; children without depression Ages 7 to 13 y.o.

Study	Reason for exclusion
	<p>Baseline wetting. Mentions several tests and the importance of quantifying and qualifying leakage but did not specify how these were applied, ie. authors did not describe the protocol to evaluate the leakages</p> <p>A (Imipramine)</p> <p>B (Placebo)</p> <p>C (Propantheline)</p> <p>Duration of treatment</p> <p>Duration of treatment, dividing on 3 arms of the study, from initial assessment until its end, was only 30 days, during the blinding-phase.</p> <p>Duration of follow up</p> <p>Is not clear</p> <p>No useable data reported</p>
McConaghy 1969	<p>RCT: Yes but excluded because children were moved between trial arms, data therefore unreliable</p> <p>Comparison group: Yes</p> <p>Organic causes excluded: No</p> <p>Systematic baseline measurement of wetting: No</p> <p>Systematic outcome measures: Yes</p> <p>Interventions: imipramine, amphetamine, pad-and-bell conditioning and random awakening</p>
Metin 1992	<p>RCT: No</p> <p>Comparison group: Yes</p> <p>Systematic baseline measurement of wetting: Yes</p> <p>Organic causes excluded: Yes</p> <p>Intervention: Diclofenac sodium suppositories (Voltaren) and glycerol suppositories</p>
Mikkelsen 1980	Outcomes not usable for this review
Misselwitz 1999	<p>RCT: Yes, but in enuretic children with urodynamically proven urge incontinence</p> <p>Intervention: oxybutynin, placebo, biofeedback</p>
Naglo 1979	<p>RCT: Yes (double-blind crossover) but in children with neurogenic bladders</p> <p>Interventions: alprenolol, placebo</p>
Nentwich 1986	<p>RCT: No</p> <p>Comparison group: Yes</p> <p>Systematic baseline measurement of wetting: Yes</p> <p>Organic causes excluded: Yes</p> <p>Intervention: Propiverin (Mictonettes)</p>
Otto-Unger 1985	<p>RCT: No</p> <p>Comparison group: Yes</p> <p>Systematic baseline measurement of wetting: Yes</p> <p>Organic causes excluded: Yes</p> <p>Intervention: propiverine hydrochloride (mictonorm/mictonets, Mictoretten)</p>
Persson-Juneman 1993	<p>RCT: No</p> <p>Comparison group: No</p> <p>Organic causes excluded: Yes</p> <p>Systematic baseline measurement of wetting: No</p> <p>Systematic outcome measures: Yes</p> <p>Interventions: Oxybutinin</p>

Study	Reason for exclusion
Polak 1981	RCT: No Comparison group: Yes Organic causes excluded: No Systematic baseline measurement of wetting: No Systematic outcome measures: No Interventions: Syndocarb, imipramine, methylphenidate, psychotherapy
Rapoport 1978	Study relates to the analysis of plasma levels of imipramine as the main outcome
Rapoport 1980	RCT: No. 2 studies, using crossover design but not randomised. Comparison group: Yes Organic causes excluded: Yes Systematic baseline measurement of wetting: Yes Systematic outcome measures: Yes Intervention: Tricyclics (imipramine, desmethylimipramine); methscopolamine
Rodriguez 2001	RCT: yes, but only for children 7 years and above Children below 7 years non randomised Oxybutynin used a sequential treatment for the non-randomised arm No drugs used in the randomised arms (only alarms and desmopressin)
Saeedalzakerin 2000	Main study outcome is parents' behaviour. Not an RCT. Abstract only
Singh 1980	RCT: No Comparison group: Yes Organic causes excluded: No Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Medical, psychological and combined
Site 1974	RCT: No Comparison group: Yes Organic causes excluded: Yes Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Imipramine, antispasmodic and sedative
Soulayrol 1970	RCT: No Comparison group: Yes Organic causes excluded: No Systematic baseline measurement of wetting: Yes Systematic outcome measures: Yes Interventions: Afranil, Dolibrax
Szabo 1999	RCT- no trial of tofisopam in daytime urgency and wetting Nocturnal enuresis not studied
Szabo 2002	RCT: unsure trial of tofisopam versus oxybutynin in daytime urgency and wetting Nocturnal enuresis not studied

Study	Reason for exclusion
Thompson 1976	RCT: Yes (double-blind crossover study) but in enuretic children with 'uninhibited vesical activity' (assumed to be detrusor overactivity) Intervention: Oxybutinin, placebo
Thorup 1982	RCT: Yes (double blind crossover trial) but many of the children had unstable bladder or diurnal enuresis or both Intervention: Emepronium bromide, placebo
Tiptaft 1984	RCT: No Comparison group: No Organic causes excluded: Yes Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Mazindol
Ulf 1964	RCT: No Comparison group: Yes Organic causes excluded: No Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Preparyl, tofranil and tryptizol
Van Hoeck 2007	Design RCT Systematic baseline measure of wetting NO Organic causes excluded YES Daytime wetting specifically excluded? Not mentioned Setting/recruitment: Hospital based Excluded because same patients included in another report with a longer follow-up (Van Hoeck 2008). A team decision was made to treat these two as a single trial.
Wasz-Hockert 1971	RCT: No Intervention: Nitrazepam, placebo
Werry 1977	RCT: No Comparison group: Yes Organic causes excluded: No Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Imipramine and chlordiazepoxide
Wilken-Jensen 1959	RCT: No Comparison group: Yes Organic causes excluded: No Systematic baseline measurement of wetting: Yes Systematic outcome measures: Yes Interventions: Banthine, probanthine
Xiao 1997	42 children with nocturnal enuresis treated by acupuncture not drugs
Yamanishi 1988	RCT: No Comparison group: Yes Organic causes excluded: No Systematic baseline measurement of wetting: Yes Systematic outcome measures: No

Study	Reason for exclusion
	Interventions: Drugs and bladder training
Young 1965	<p>RCT: No Comparison group: Yes Organic causes excluded: Yes Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: CNS stimulants and conditioning (alarms)</p>
Yurdakok 1986	<p>RCT (groups randomly assigned) Systematic baseline measure of wetting: No Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Setting: Paediatric OP, Ankara, Turkey</p> <p>No. of children (boys): 41 (25) Incl: age at least 6 years, suitable for drug treatment, nocturnal enuresis Excl: urine abnormality Previous treatment: most had failed with simple methods such as waking or fluid restriction Ages: 6-16 years (mean 11 years)</p> <p>A (14): imipramine 25mg B (8): amitriptyline 25 mg C (10): chlorthalidone 5mg/2.5mg D (9): piracetam 400 mg Duration of treatment: 6 weeks Imipramine significantly better than amitriptyline, chlorthalidone and piracetam on therapeutic index score: A: 1.57, B: 1.25, C: 1.3, D: 0.33</p> <p>No useable data Groups comparable at baseline on age and social class</p>
Zou 2008	acupuncture not drugs

Characteristics of studies awaiting assessment *[ordered by study ID]*

Cupalova-Naglova 1968

Methods	Awaiting translation
Participants	
Interventions	
Outcomes	
Notes	

DATA AND ANALYSES

Comparison 1. Drugs versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 phenmetrazine vs placebo	1	20	Mean Difference (IV, Random, 95% CI)	1.00 [-2.52, 0.52]
1.2 indomethacin suppository vs placebo	2	92	Mean Difference (IV, Random, 95% CI)	-3.09 [-4.23, -1.96]
1.3 diclofenac sodium vs placebo	1	40	Mean Difference (IV, Random, 95% CI)	-4.21 [-5.76, -2.66]
1.4 diazepam vs placebo	1	50	Mean Difference (IV, Random, 95% CI)	-4.87 [-6.25, -3.49]
1.5 ibuprofen vs placebo	1	151	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.01, 0.21]
1.6 pseudoephedrine vs placebo	1	145	Mean Difference (IV, Random, 95% CI)	0.10 [-0.51, 0.71]
1.7 ibuprofen + pseudoephedrine	1	153	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.48, -0.12]
1.8 tolterodine vs placebo	1	39	Mean Difference (IV, Random, 95% CI)	-0.70 [-2.01, 0.61]
1.9 scopolamine butyl bromide vs placebo	1	28	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.56, 1.16]
2 Number of wet nights per week (no SDs)			Other data	No numeric data
2.1 amphetamine sulphate/ephedrine + atropine vs placebo			Other data	No numeric data
2.2 furosemide vs placebo			Other data	No numeric data
2.3 meprobamate vs placebo			Other data	No numeric data
2.4 propantheline bromide vs placebo			Other data	No numeric data
2.5 emepronium vs placebo			Other data	No numeric data
2.6 indoramin 20 mg vs placebo			Other data	No numeric data
2.7 indoramin 10 mg vs placebo			Other data	No numeric data
2.8 propantheline vs placebo			Other data	No numeric data
2.9 LA tolterodine +desmo vs placebo + desmo			Other data	No numeric data
3 Number not achieving 14 consecutive dry nights	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 chlorprotixine vs placebo	1	90	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.85, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 indomethacin suppository vs placebo	1	38	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.16, 0.79]
3.3 diclofenac vs placebo	3	124	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.34, 1.13]
3.4 meprobamate vs placebo	1	67	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.92, 1.35]
3.5 hydroxyzine chloride vs placebo	1	80	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.97]
3.6 methylphenidate hydrochloride vs placebo	1	83	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.67, 0.94]
3.7 atropine sulphate + ephedrine sulphate vs placebo	1	50	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.71, 1.41]
3.8 chlordiazepoxide + amitriptyline vs placebo	1	215	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]
3.9 piracetam vs placebo	1	32	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.91, 2.11]
3.10 propantheline vs placebo	2	226	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.95, 1.05]
3.11 oxybutinin vs placebo	1	39	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.52, 1.24]
3.12 diazepam vs placebo	1	50	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.11, 0.46]
3.13 propantheline vs placebo	1	15	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.15, 11.64]
3.14 atomoxetine vs placebo	1	83	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.70, 0.95]
3.15 hychlorthiazide vs placebo	1	64	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.84, 1.04]
3.16 LA tolterodine + desmo vs placebo + desmo	1	34	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.70, 1.13]
3.17 mesterolone vs placebo	1	30	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.17, 0.62]
3.18 tolterodine vs placebo	1	50	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.93, 1.08]
3.19 oxybutynin + alarm vs placebo + alarm	1	55	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.56, 1.65]
3.20 oxybutynin + holding exercises + alarm vs placebo + holding exercises + alarm	1	54	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.58, 1.75]
3.21 New Subgroup	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Number failing or relapsing after end of treatment	5		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 atropine sulphate + ephedrine sulphate vs placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 chlordiazepoxide + amitriptyline vs placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 oxybutinin vs placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 mesterolone vs placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 oxybutynin + alarm vs placebo + alarm	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 oxybutynin + holding exercises + alarm vs placebo + holding exercises + alarm	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Number of wet nights per week after treatment stopped (no SDs)			Other data	No numeric data
5.1 propantheline bromide vs placebo			Other data	No numeric data

Analysis 1.1. Comparison 1 Drugs versus placebo, Outcome 1 Number of wet nights per week.

Study or subgroup	Active drug		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.1.1 phenmetrazine vs placebo							
Harrington 1960#	10	1.8 (1.8)	10	2.8 (1.7)		100%	-1[-2.52,0.52]
Subtotal ***	10		10			100%	-1[-2.52,0.52]
Heterogeneity: Not applicable							
Test for overall effect: Z=1.29(P=0.2)							
1.1.2 indomethacin suppository vs placebo							
Al-Waili 1989#	19	2.5 (2.5)	19	6.2 (1.3)		46.67%	-3.71[-4.96,-2.46]
Sener 1998	29	2.6 (2.2)	25	5.1 (2)		53.33%	-2.55[-3.66,-1.44]
Subtotal ***	48		44			100%	-3.09[-4.23,-1.96]
Heterogeneity: Tau ² =0.31; Chi ² =1.85, df=1(P=0.17); I ² =45.87%							
Test for overall effect: Z=5.34(P<0.0001)							
1.1.3 diclofenac sodium vs placebo							
Al-Waili 1986#	20	1.9 (1.5)	20	6.2 (3.2)		100%	-4.21[-5.76,-2.66]
Subtotal ***	20		20			100%	-4.21[-5.76,-2.66]
Heterogeneity: Not applicable							
Test for overall effect: Z=5.32(P<0.0001)							
1.1.4 diazepam vs placebo							
Kline 1968	28	1 (2.5)	22	5.9 (2.4)		100%	-4.87[-6.25,-3.49]
Subtotal ***	28		22			100%	-4.87[-6.25,-3.49]
Heterogeneity: Not applicable							
Test for overall effect: Z=6.91(P<0.0001)							
					-5		
					-2.5		
					0		
					2.5		
					5

Analysis 1.2. Comparison 1 Drugs versus placebo, Outcome 2 Number of wet nights per week (no SDs).

Study	Number of wet nights per week (no SDs)	
	Drug	Placebo
amphetamine sulphate/ephedrine + atropine vs placebo		
Wright 1974	Mean = 4.1, N=8	Mean = 3.5, N=10
furosemide vs placebo		
Moltke 1979	Mean = 5.11, N=41	Mean = 4.69, N=44
meprobamate vs placebo		
Breger 1961	Mean = 3.26, N=34	Mean = 3.21, N=33
propantheline bromide vs placebo		
Leys 1956	Mean = 4.7, N=33	mean = 5.36, N=32
emeprium vs placebo		
Petersen 1974#	Mean = 4.36, N=61	Mean = 4.37, N=61
indoramin 20 mg vs placebo		
Shaffer 1978#	Mean = 2.6, N=14	Mean = 2.68, N=14
indoramin 10 mg vs placebo		
Shaffer 1978#	Mean = 2.5, N=14	Mean = 2.68, N=14
propantheline vs placebo		

Study	Number of wet nights per week (no SDs)	
	Drug	Placebo
Mayon-White 1956	Mean = 2.11, n=9	Mean = 1.75, n=6
LA tolterodine +desmo vs placebo + desmo		
Austin 2008	mean = 3, n= 18	mean = 5, n=16

Analysis 1.3. Comparison 1 Drugs versus placebo, Outcome 3 Number not achieving 14 consecutive dry nights.

Analysis 1.4. Comparison 1 Drugs versus placebo, Outcome 4 Number failing or relapsing after end of treatment.

Analysis 1.5. Comparison 1 Drugs versus placebo, Outcome 5 Number of wet nights per week after treatment stopped (no SDs).

Number of wet nights per week after treatment stopped (no SDs)		
Study	Drug	Placebo
propantheline bromide vs placebo		
Leys 1956	Mean = 4.96, N=33	Mean = 5.33, N=32

Comparison 2. Drug - drug comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week	9		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 meprobamate + hydroxyzine vs imipramine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 ephedrine sulphate vs imipramine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 indomethacin suppository vs desmopressin (nasal drops)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 oxybutinin vs pseudoephedrine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 oxybutinin vs indomethacin	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 oxybutinin vs dicyclomine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.7 pseudoephedrine vs indomethacin	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.8 desmopressin + oxybutynin vs desmopressin	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.9 desmopressin + oxybutynin vs imipramine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.10 oxybutynin vs imipramine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.11 oxybutynin vs oxybutynin + imipramine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.12 oxybutynin + imipramine vs imipramine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.13 tolterodine vs imipramine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.14 scopolamine butyl bromide vs imipramine	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.15 New Subgroup	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Number of wet nights per week (no SDs)			Other data	No numeric data
2.1 furosemide vs imipramine			Other data	No numeric data
2.2 triclofos vs ephedrine			Other data	No numeric data
2.3 emepronium vs imipramine			Other data	No numeric data
2.4 emepronium vs imipramine-N-oxide			Other data	No numeric data
2.5 indoramin 20 mg vs indoramin 10 mg			Other data	No numeric data
3 Number not achieving 14 consecutive dry nights	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 meprobamate + hydroxyzine vs imipramine	1	25	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.04, 2.69]
3.2 hydroxyzine chloride vs methylphenidate hydrochloride	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.30]
3.3 triclofos vs ephedrine	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.07]
3.4 diclofenac vs desmopressin (nose drops)	1	62	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.13, 3.33]
3.5 oxybutinin vs imipramine	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.76, 1.26]
3.6 oxybutinin vs imipramine + oxybutinin	2	100	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.06, 2.01]
3.7 propantheline vs propantheline + phenobarbitone	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.96, 1.24]
3.8 oxybutynin + imipramine vs imipramine	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.50, 0.94]
3.9 tolterodine vs imipramine	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.01, 1.53]
3.10 desmopressin + oxybutynin vs imipramine	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.44, 0.80]
3.11 desmopressin + oxybutynin vs desmopressin	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.58, 1.16]
3.12 diclofenac vs imipramine	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.81, 1.30]
3.13 diclofenac vs diclofenac + imipramine	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.92, 1.50]
4 Number failing or relapsing after treatment stopped	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 meprobamate + hydroxyzine vs imipramine	1	25	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.90, 1.59]
4.2 oxybutinin vs imipramine	2	64	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.60, 1.24]
4.3 oxybutinin vs imipramine + oxybutinin	2	81	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [1.23, 3.28]
4.4 oxybutynin + imipramine vs imipramine	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.16, 0.77]

Analysis 2.1. Comparison 2 Drug - drug comparisons, Outcome 1 Number of wet nights per week.

Analysis 2.2. Comparison 2 Drug - drug comparisons, Outcome 2 Number of wet nights per week (no SDs).

Study	Number of wet nights per week (no SDs)	
	Drug 1	Drug 2
	furosemide vs imipramine	

Study	Number of wet nights per week (no SDs)	
	Drug 1	Drug 2
Moltke 1979	Mean = 5.11, N=41	Mean = 3.43, N=43
triclofos vs ephedrine		
GP Research Gp 1970#	Mean = 4.1, N=28	Mean = 4.5, N=27
emepronium vs imipramine		
Petersen 1974#	Mean = 4.36, N=61	Mean = 2.4, N=61
emepronium vs imipramine-N-oxide		
Petersen 1974#	Mean = 4.36, N=61	Mean = 3.24, N=61
indoramin 20 mg vs indoramin 10 mg		
Shaffer 1978#	Mean = 5.2, N=14	Mean = 4.99, N=14

Analysis 2.3. Comparison 2 Drug - drug comparisons, Outcome 3 Number not achieving 14 consecutive dry nights.

Analysis 2.4. Comparison 2 Drug - drug comparisons, Outcome 4 Number failing or relapsing after treatment stopped.

Comparison 3. Drug versus behavioural interventions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week	0		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Number of wet nights per week (no SDs)			Other data	No numeric data
2.1 amphetamine sulphate/ephedrine + atropine vs alarm			Other data	No numeric data
3 Number not achieving 14 consecutive dry nights	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 amphetamine vs alarm	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 methedrine + alarm vs alarm	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 piracetam vs play + supportive therapy	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 piracetam vs piracetam + play + supportive therapy	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 oxybutynin vs accupressure	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Number failing or relapsing after end of treatment	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Number of wet nights per week after treatment stopped (no SDs)	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.2. Comparison 3 Drug versus behavioural interventions, Outcome 2 Number of wet nights per week (no SDs).

Study	Number of wet nights per week (no SDs)	
	Drug	Behavioural method
	amphetamine sulphate/ephedrine + atropine vs alarm	
Wright 1974	Mean = 4.1, N=8	Mean = 1.7, N=10

Analysis 3.3. Comparison 3 Drug versus behavioural interventions, Outcome 3 Number not achieving 14 consecutive dry nights.

Study or subgroup	Drug n/N	Behavioural n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.3.1 amphetamine vs alarm				
Forrester 1964	14/17	6/16		2.2[1.12,4.29]
3.3.2 methedrine + alarm vs alarm				

favours drug 0.1 0.2 0.5 1 2 5 10 favours behavioural

Comparison 5. Combination therapy versus monotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number not achieving 14 dry nights	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Tolterodine + desmopressin vs Desmopressin	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.70, 1.13]
1.2 Oxybutynin + desmopressin vs Desmopressin	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.63, 1.31]
1.3 Oxybutynin + Imipramine vs Imipramine	2	101	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.50, 0.92]
1.4 Oxybutynin + Alarm vs Placebo + Alarm	1	55	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.56, 1.65]
1.5 Anticholinergic + desmopressin vs Desmopressin	2	131	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.70, 1.16]
2 Number failing or relapsing after end of treatment	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Oxybutynin + Imipramine vs Imipramine	2	85	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.31, 0.74]
2.2 Oxybutynin + Alarm vs Placebo + Alarm	1	52	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.75, 2.78]

Analysis 5.1. Comparison 5 Combination therapy versus monotherapy, Outcome 1 Number not achieving 14 dry nights.

Analysis 5.2. Comparison 5 Combination therapy versus monotherapy, Outcome 2 Number failing or relapsing after end of treatment.

WHAT'S NEW

Date	Event	Description
24 October 2012	New search has been performed	This is the fourth update of this review. Ten new trials were added to the previous version (Alawwa 2010#; Austin 2008; el-Sadr 1990a; Esmaeili 2008; Gelotte 2009; Korczyn 1979#; Lee 2005; Neveus 2008#; Van Hoeck 2008; Yuksek 2003). Of these trials, five focused on the role of anticholinergic medications as supplementary therapy (Austin 2008; Esmaeili 2008; Neveus 2008#; Van Hoeck 2008; Yuksek 2003).
24 October 2012	New citation required but conclusions have not changed	This is the fourth update of this review. Ten new trials were added to the previous version (Alawwa 2010#; Austin 2008; el-Sadr 1990a; Esmaeili 2008; Gelotte 2009; Korczyn 1979#; Lee 2005; Neveus 2008#; Van Hoeck 2008; Yuksek 2003). Of these trials, five focused on the role of anticholinergic medications as supplementary therapy (Austin 2008; Esmaeili 2008; Neveus 2008#; Van Hoeck 2008; Yuksek 2003).

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 3, 2000

Date	Event	Description
25 September 2008	Amended	Converted to new review format.
17 June 2007	New search has been performed	Minor update Issue 2, 2008. One new trial included, one new study excluded

Date	Event	Description
24 August 2005	New search has been performed	Minor update Issue 4, 2005. One further trial excluded, no change in conclusions.
25 August 2003	New citation required and conclusions have changed	Substantive update Issue 4, 2003. Twenty five new trials added in addition to the seven in the original review. Conclusions revised.

CONTRIBUTIONS OF AUTHORS

The review authors (AD and PC) independently assessed the studies identified by the updated searches and extracted data from the included studies. AD and PS also reviewed the included studies from the previous review and updated the risk of bias tables. AD and PC analysed the data and wrote the updated review.

DECLARATIONS OF INTEREST

None declared

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol included trials which investigated drugs other than desmopressin and tricyclics for nocturnal enuresis in children. A large variety of drugs have been studied across many pharmacological groups. The authors have deviated from the protocol on the issue of dealing with trials which include children with daytime wetting or other lower urinary tract symptoms. Following the guidelines drafted by the ICCS, we have now treated nocturnal enuresis with daytime symptoms as non-monosymptomatic enuresis and have hence included these trials in the review as long as they focused on outcomes relevant to this review. A subgroup analysis investigating the efficacy of combination therapy with anticholinergics compared to monotherapy was undertaken (Comparison 5).

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; Antidiuretic Agents [*therapeutic use]; Cholinergic Antagonists [therapeutic use]; Clinical Alarms [adverse effects]; Drug Therapy, Combination [methods]; Nocturnal Enuresis [*drug therapy] [prevention & control]; Psychotropic Drugs [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Humans