Evidence Extractions

Question: What are the core elements of initial clinical history and examination, in the evaluation of children and young people under 19 years old who have nocturnal enuresis?

Grading: 2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

Butler R;Holland P;Devitt H;Hiley E;Roberts G;Redfern E;

The effectiveness of desmopressin in the treatment of childhood nocturnal enuresis: predicting response using pretreatment variables

Ref ID 774 1998

Study Type Cohort **Funding** Ferring Pharmaceuticals

Number of participant	66 children
Inclusion/Exclusion Criteria	Inclusion: Aged 8 to 16 years, wet at least 4 times over 4 weeks, no associated daytime wetting, primary NE – never been dry for more than 6 months, normal clinical examination with no neurological or urological cause for the enuresis, not statemented for learning difficulties, not undergoing enuresis-related treatment, and parental and child consent given.
Patient Characteristics	54 boys and 12 girls. Mean age was 10.4 (SD 1.7) years and age range 8.1 to 14.5 years.
Recruitment	Referred as outpatients for monosymptomatic NE.
Setting	Leeds, UK.
Interventions/ Test/ Factor being investigated	Child and parental factors.
Comparisons	No comparison
Length of Study/ Follow-up	No follow up
Outcome measures studied	Factors affecting treatment outcomes.
Results	Child measures: impact on lifestyle, beliefs about bedwetting, perceived intolerance, self image, self esteem and self-perception profile. Parental measures: concerns, beliefs about bedwetting, revised maternal intolerance scale, attitudes to bedwetting, efforts to treat NE, maternal self esteem and perceived stress scale. The measures were collected at a pre-clinic home visit or first clinic visit. There were no statistically significant differences in patients between any of the measures. Children had 20 micrograms intranasal or 0.2 mg oral desmopressin for 2 weeks, parents were then instructed to double the dose. A follow up appointment was at 4 weeks. The study showed the following were significant in predicting outcome: severity of wetting before treatment, child's birth weight, child's perception of maternal intolerance, the perceived impact on the child's life (situational), parental belief that the enuresis is a physical problem, that it will go on for years and that the child wets the bed to retaliate against the parent. The following were not significant in predicting outcome: age, sex, demographic or situational variables.
Safety and adverse effects	None reported.

Does the study answer the question?	The study showed the following were significant in predicting outcome: severity of wetting before treatment, child's birth weight, child's perception of maternal intolerance, the perceived impact on the child's life (situational), parental belief that the enuresis is a physical problem, that it will go on for years and that the child wets the bed to retaliate against the parent.
Effect due to factor in study?	The study identified significant predictors of treatment outcome.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had primary NE and a mean age of 10.4 years.
Internal Validity	Not addressed

Butler RJ;Brewin CR;Forsythe W;

Relapse in children treated for nocturnal enuresis: prediction of response using pre-treatment variables

Ref ID 1500 1990

Study Type Cohort **Funding** Not reported

Number of participant	37 patients (n=24 who had been treated with modified dry bed training and n=13 had been treated with an alarm).
Inclusion/Exclusion Criteria	Inclusion: successfully treated (achieved 14 consecutive dry nights) within 16 weeks of treatment with an alarm or modified dry bed training.
Patient Characteristics	28 boys, 9 girls; the mean age was 9.6 years (age range 6.1 to 12.4 years) at the time of treatment; 83.8% had primary NE, 16.2% had secondary NE; 24 had been treated with modified dry bed training, 13 had been treated with an alarm
Recruitment	Patients successfully treated with alarm or modified dry bed training, and followed up.
Setting	Leeds, UK.
Interventions/ Test/ Factor being investigated	Pre-treatment assessment variables predicting relapse.
Comparisons	Between children who relapsed and children who did not relapse.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Predicting relapse.
Results	The study conducted a parent-child interview – age, wetting history, presence of urgency, frequency and action previously adopted to control bedwetting; maternal questionnaire on bed wetting – maternal beliefs of cause, attribution, feelings, concerns over bed wetting; tolerance scale (Morgan and Young, 1975); child interview – beliefs and reactions to bedwetting. The treatment outcomes were speed of acquisition to dryness, and persistence of dryness. The study conducted 2 sets of follow-up appointments, 6 at 4 week intervals to find out the number of wet nights, the other a long term follow-up by questionnaire. The study combined children who relapsed after modified dry bed training and children who relapsed after alarm therapy, In total 13 children relapsed (10 were originally treated with modified dry bed training and 3 were originally treated with alarm therapy) The study showed children who relapsed were more likely to have had more wet

	nights over the 16 weeks of treatment (p<0.05); more likely to attribute their bed wetting to drinking too much prior to going to bed (p<0.05); less likely to attribute it to being too cold to arise from the bed during the night (p<0.05); more likely to have a history of secondary NE (p<0.001); and more likely not to worry over the bedwetting (p<0.01). The study states only more likely to have a history of secondary NE and more likely not to worry over the bedwetting can be regarded with any degree of confidence as the alpha level should be set no higher than p<0.01 with 78 comparisons.
Safety and adverse effects	None reported
Does the study answer the question?	The study reports children who relapsed were more likely to have a history of secondary NE and more likely not to worry over the bedwetting. There was a small correlation that children who relapsed were more likely to have had more wet nights over the 16 weeks of treatment, more likely to attribute their bed wetting to drinking too much prior to going to bed and less likely to attribute it to being too cold to arise from the bed during the night.
Effect due to factor in study?	The study identified predictors for relapse.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had been sucessfully treated with alarms of DBT and had a mean age of 9.6 years.

Internal Validity

Butler RJ;Holland P;Robinson J;

Examination of the structured withdrawal program to prevent relapse of nocturnal enuresis

Ref ID 527 2001

Study Type Cohort **Funding** Leeds Metropolitan University.

Number of participant	51 patients
Inclusion/Exclusion Criteria	Inclusion: at least 90% dry nights while on medication (desmopressin or imipramine), on medication for at least 4 months, no neurological or urological cause of NE, and vulnerable to relapse due to at least 2 unsuccessful attempts at medication withdrawal by gradual dose tapering.
Patient Characteristics	37 were boys and 14 girls. Mean age was 11.8 (sd 2.06) years and age range 7.7 to 15.9 years. 37 children were treated with desmopressin and 14 with imipramine. The mean length of treatment was 10.6 (sd 5.04) months (range 4 to 24 months). The doses of desmopressin were 8 children on 10 micrograms, 17 on 20 micrograms or 0.2 mg, 9 on 40 micrograms or 0.4 mg, 2 on 60 micrograms or 0.6 mg and 1 on 80 micrograms. The doses of imipramine were 10 on 25 mg, 2 on 50 mg and 2 on 75 mg.
Recruitment	Not reported.
Setting	Leeds, UK
Interventions/ Test/ Factor being investigated	Factors predicting response to structured withdrawal program.
Comparisons	No comparison.
Length of Study/ Follow-up	6 month follow up.
Outcome measures studied	Factors predicting response to structured withdrawal program.

Results	The withdrawal program started during week 1 on taking medication on day 1, 3, 4 and 6; in week 2 on days 1, 2, 4 and 7; in week 3 on days 2 5 and 7; in week 4 on days 1, 3 and 6; in weeks 5 on days 2 and 5; in week 6 on days 2 and 6; in week 7 on days 3 and 7 and in week 8 on day 4. Alarm treatment was offered on medication free nights. 38 children stayed dry during weeks 9 and 10, 72.2% of these remained dry at 6 months. The study showed there was no association between the types of medication and outcome at weeks 9 and 10 (p=0.303) or at 6 months (p=0.667). At weeks 9 and 10 success was associated with a higher number of dry medication nights (p=0.011) and no mediation nights (p=0.002). At weeks 9 and 10 there was no association between success and age (p=0.057), gender (p=0.259), use of the alarm (p=0.976), dose level of desmopressin (p=0.7) or imipramine (p=0.65), duration of treatment before withdrawal (p=0.760). At 6 months success was associated with a higher number of dry medication nights (p=0.005) and no mediation nights (p=0.008).
Safety and adverse effects	None reported.
Does the study answer the question?	At weeks 9 and 10 and at 6 months success was associated with a higher number of dry medication nights and no medication nights.
Effect due to factor in study?	Study showed a structured withdrawal program could increase continued dryness.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had a mean age of 11.8 years.

Internal Validity

Butler RJ;Redfern EJ;Forsythe WI;

The child's construing of nocturnal enuresis: a method of inquiry and prediction of outcome

Ref ID 1215 1990

Study Type Cohort **Funding** Not reported.

Number of participant	45 patients with nocturnal enuresis
Inclusion/Exclusion Criteria	Inclusion: aged over 6 years, wet at least 4 times a month, normal examination, normal urine microscopy, normal intelligence, not undergoing any enuresis related treatment, living with natural parent(s).
Patient Characteristics	42 boys and 13 girls. The mean age was 10.2 (sd 2.04) years, age range 6.9 to 14.7 years, and 4 children had associated diurnal enuresis.
Recruitment	Referred as outpatients because of NE.
Setting	Out-patients, UK.
Interventions/ Test/ Factor being investigated	Tolerance scale and child interview.
Comparisons	Treatment success with an alarm.
Length of Study/ Follow-up	No follow up.

Outcome measures studied	Factors relating to treatment success with an alarm.
Results	The study examined – tolerance scale, child interview – anticipation of change, resistance to change, perceived family reactions, secrecy. Children were treated with an alarm and were encouraged to waken quickly, remove and dry sensitive plate, switch off the alarm and use the toilet to complete urination; the child was required to remove wet clothes and sheets and replace them with dry ones and reset the alarm. Treatment was for 16 weeks. 4 children dropped out and excluded from results, and 2 children had missing outcome measures. There was no statistically significant difference in ages or between males and females, but maternal intolerance was significantly higher in males than females. 65.3% were successfully treated. The study showed age was a significant predictor of response, but maternal intolerance, sex or presence of diurnal enuresis was not related to response. The presence of resistance constructs and the absence of perceived family support were significant predictors of treatment failure ($p<0.05$). The following were not predictors of treatment failure: perceived family intolerance, teased by siblings and secrecy. The study showed the probability of successful treatment increases with age but decreases with the presence of resistance constructs.
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that the probability of successful treatment increased with age but decreased with the presence of resistance constructs.
Effect due to factor in study?	Study identified significant predictors of treatment response.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had a mean age of 10.2 years.

Internal Validity

Butler RJ;Robinson JC;Holland P;Doherty-Williams D;

Investigating the three systems approach to complex childhood nocturnal enuresis--medical treatment interventions

Ref ID 331 2004

Study Type Cohort **Funding** Ferring Pharmaceuticals, UK

Number of participant	66 patients
Inclusion/Exclusion Criteria	Inclusion: aged 5 to 16 years old, wetting at least 4 times a week, no major daytime wetting, attending mainstream school, no neurological or urological problems, and parents and child consented.
Patient Characteristics	44 males and 22 females with a mean age of 10.41 years (sd 2.38). 47 had primary Ne, 16 had secondary NE, 63.6% had no dry nights during 14 night baseline, 18.2% had 1 to 2 dry nights, 9.1% had 3 to 6 dry nights, 24 had multiple wetting and 11 did not have multiple wetting. 29 had a family history of NE, 12 did not have a family history of NE, 57.4% had tried alarms, 51.8% had tried desmopressin 9.5% had tried imipramine, 11.9% had tried oxybutynin and 16.7% had tried other treatments.
Recruitment	Referred as outpatients for NE.

Setting	Leeds, UK
Interventions/ Test/ Factor being investigated	3 systems approach
Comparisons	No comparison.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Dryness (assessed on a banding scale where dry nights were judged against number of nights).
Results	The three system approach was used to obtain information on 6 clinical signs – urgency, frequency, passes small voids, wakes after wetting, small or variable wet patches, or wets soon after sleep. Parents answered often or rarely to each sign. The study also recorded demographics, school attended, family history, birth weight, mothers age at birth, early feeding practice, child's weight and height, presence of other predictive factors, and previous and current treatments. If children scored on 2 or more items representing bladder overactivity they were described as non-monosymptomatic and prescribed 5 to 10 mg oxybutynin or ditropan for 4 weeks. Iif the child did not have 2 or more signs they were described as monosymptomatic and prescribed 0.4 mg desmopressin for 4 weeks. Treatment was continued for a further 4 weeks if success criterion (of >50 reduction in number of wet nights) was met. If children did not meet the success criterion they were prescribed desmopressin and anticholinergics. 13 children dropped out In the desmopressin group of 42 children (7 were missing) 7 children achieved no dry nights, 4 children achieved 1 to 24% dry nights, 7 children achieved 25 to 49% dry nights, 10 children achieved 50 to 89% dry nights and 7 children achieved 90 to 100% dry nights. In the anticholinergic group of 24 children (6 were missing) 3 children achieved no dry nights, 6 children achieved 1 to 24% dry nights, 3 children achieved 25 to 49% dry nights, 5 children achieved 50 to 89% dry nights and 1 child achieved 90 to 100% dry nights. In the desmopressin and anticholinergic group of 30 children (2 were missing) 5 children achieved no dry nights, 5 children achieved 1 to 24% dry nights, 3 children achieved 25 to 49% dry nights, 10 children achieved 50 to 89% dry nights and 5 children achieved 90 to 100% dry nights. The study showed there were no predictive factors for response to desmopressin, although 50% of children wet soon after sleep. For anticholinergics medication the predictive factors were age ($p = 0.03$), frequency ($p = 0.01$), passing small voids ($p = 0.03$), small or variable wet patches ($p = 0.029$) and wakes soon after voiding ($p = 0.062$). There were no predictive variables for the combination group.
Safety and adverse effects	None reported
Does the study answer the question?	The study showed there were no predictive factors for response to desmopressin, although 50% of children wet soon after sleep. For anticholinergics medication the predictive factors were age, frequency, passing small voids, small or variable wet patches and wakes soon after voiding. There were no predictive variables for the combination group.
Effect due to factor in study?	Study identified predictive factors for treatment outcome with anticholinergics.
Consistency of results with other studies?	No other similar studies.

Directly applicable to guideline population?	Children had a mean age of 10.41 years.

Internal Validity

Cayan S;Doruk E;Bozlu M;Duce MN;Ulusoy E;Akbay E;

The assessment of constipation in monosymptomatic primary nocturnal enuresis

Ref ID 3910 2001

Study Type Cohort **Funding** Not reported.

Number of participant	5350 patients surveyed. 679 found to have primary NE. 125 of the 679 with primary enuresis attended for interview and ultrasound scan. There were 4671 controls (no enuresis).
Inclusion/Exclusion Criteria	Inclusion: primary monosymptomatic NE, wetting 2 or more times a week. Exclusion: secondary NE, neurological abnormalities, history of colon surgery, bowel disease, developmental delay, or metabolic disease.
Patient Characteristics	Primary NE group: the mean age was 9.23 years (sd 2.36) and 59.6% were male. Control group the mean age was 9.14 years (sd 2.89) and 59.6% were male.
Recruitment	Day care centres and primary and secondary schools between October 1998 and August 1999.
Setting	Both rural and urban areas of Turkey.
Interventions/ Test/ Factor being investigated	Diagnosis of constipation.
Comparisons	Comparison between proportion of children with enuresis who were constipated and proportion of controls with constipation.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Diagnosis of constipation.
Results	Children were sent a questionnaire about micturition and defecation habits (82.3% response rate). Children with NE were invited to attend a hospital to undergo a neurological examination (physical examination, electroencephalogram if needed, serum creatinine levels) and abdominal sonogram (plain abdominal film), which 125 out of 679 attended. All children had normal serum creatinine levels and renal sonograms. Constipation was described as less than 3 bowel movements a week for at least 6 months There was a statistically significant difference in the number of children with constipation between the children with NE (7.06%) and control children (1.45%) p = 0.000.
Safety and adverse effects	None reported.
Does the study answer the question?	There was a statistically significant difference in the number of children with constipation between the children with NE and control children.
Effect due to factor in study?	The study identified differences in constipation rates between children with NE and children without NE.
Consistency of results with other studies?	No other similar studies

Directly applicable to guideline population?	Children had primary NE and a mean age of 9.23 years.

Internal Validity

Cutler C;Middleton AWJ;Nixon GW;

Radiographic findings in children surveyed for enuresis

Ref ID 1624 1978

Study Type	Cohort	**Funding**	Not reported.

Number of participant	216 patients
Inclusion/Exclusion Criteria	Inclusion: Children with NE who were referred for intravenous pyelogram and voiding cystourethrogram between July 1974 and June 1975.
Patient Characteristics	59.3% were male. The male mean age was 7.54 years, the female mean age was 5.36 years. The mean age of males with normal studies was 7.35 years, the mean age of males with abnormal studies was 8.17 years. The mean age of females with normal studies was 7.54 years, the mean age of females with abnormal studies was 4.68 years. 47% had NE alone, 51% had NE and diurnal enuresis, 2% had diurnal enuresis alone.
Recruitment	Referred of NE for investigations between July 1974 and June 1975.
Setting	Primary Medical Centre, Utah, USA.
Interventions/ Test/ Factor being investigated	Intravenous pyelogram and voiding cystourethrogram.
Comparisons	No comparison.
Length of Study/ Follow-up	No follow up
Outcome measures studied	Radiographic abnormalities, and need for surgery.
Results	89 radiographic abnormalities were found, 59 of which were clinically significant. 31.5% of males had radiographic abnormalities and 28.4% of females had radiographic abnormalities. There were 53 cases of upper urinary tract abnormalities, 43 of which were clinically significant. The most common was vesicoureteral reflux in 32 children, 5 of which had bilateral reflux and 27 had unilateral reflux. 4 children had ureteropelvic junction obstruction, 2 had hydrocalycosis, 2 had ureterovesical junction obstruction, 1 had pyelonephritis. Other non clinically significant abnormalities identified were duplicated collecting structure (5 children), renal ectopia (2 children), malrotation (2 children) and pyelocalyceal diverticulum (1 child) 135 children had clinical data available, of these 31% had a history of UTI prior to roentgenography. 5.2% of children with NE alone had UTI, 25.2% of children with diurnal enuresis with or without Ne had UTI. 54.8% of children with UTI had abnormal radiographic findings. Surgery from radiographic findings: Children with UTI – 7 had meatotomy, internal urethrotomy or urethral dilatation for stenosis (minor surgery), 6 had bilateral or unilateral ureteroneocystostomy and 1 had posterior urethral valve destruction (major surgery). Children without UTI – 8 had meatotomy, internal urethrotomy or urethral dilatation for stenosis (minor surgery), 4 had bilateral or unilateral ureteroneocystostomy and 0 had posterior urethral valve destruction (major surgery).

	Statistical evaluation of children needing surgery Minor surgery – 0 males with UTI, 5 males without UTI, 9 females with UTI, 1 female without UTI, 5 with NE, 8 with diurnal enuresis with or without NE. the mean age was 5.6 years. Major surgery – 3 males with UTI, 2 males without UTI, 4 females with UTI, 1 female without UTI, 1 with NE, 7 with diurnal enuresis with or without NE. the mean age was 5.5 years.
Safety and adverse effects	None reported.
Does the study answer the question?	89 radiographic abnormalities were found, 59 of which were clinically significant. 31.5% of males had radiographic abnormalities and 28.4% of females had radiographic abnormalities.
Effect due to factor in study?	Study identified readiographic findings in children with NE.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Male children had a mean age of 7.54 years and females had a mean age of 5.36 years.

Internal Validity

Devlin JB;O'Cathain C;

Predicting treatment outcome in nocturnal enuresis

Ref ID 1183 1990

Study Type Cohort **Funding** Not reported

Number of participant	127 patients
Inclusion/Exclusion Criteria	Inclusion: aged 6 to 18 years, and wet at least 2 nights a week. Exclusion: overt psychiatric disturbance requiring urgent referral to the child guidance service, moderate or greater mental handicap, or urological or neurological causes of incontinence.
Patient Characteristics	The mean age was 8.8 years, age range 6 to 17 years; male:female ratio was 2:1; 11% were in socioeconomic group I, 14% in group II, 11% in group III, 32% in group IV, 25% in group V and 7% in group VI; the unemployment rate was 30% among fathers, 70% among mothers; 83% had primary NE, 17% had secondary NE; 83% had night time only wetting, 17% had night and day time wetting; 2 children had UTI, 4 had urological abnormality. 20% had a stressful event in early childhood consisting of a hospital admission (17% due to physical illness, 2% due to physical handicap, 1 % due to sexual abuse) A prior attendance at the child guidance clinic was recorded: 21% for a reactive disorder, 6% for a learning disorder, 3% for a mental handicap, 2% for developmental delay, 2% for a personality disorder and 1% for a psychosomatic disorder. 52 children admitted to stress in the family – 13 due to financial difficulties, 11 due to marital discord, 7 due to unemployment, 6 due to death in family, 6 due to other family disharmony, 2 due to serious illness in the family and 7 due a combination of the above. 9% had a family history of psychiatric illness and 18% had adverse housing conditions. 2% of parents had no concern about the bedwetting, 12% were a little concerned, 44% had moderate concern and 42% had a great deal of concern. 8% of children had no concern about the bedwetting, 26% were a little concerned, 34% had moderate concern and 32% had a great deal of concern.
Recruitment	Consecutive referrals to community based enuresis clinic from GP, paediatricians, clinical method officers and a small number from the child guidance service.
Setting	Community based clinic, Dublin, Ireland.

Interventions/ Test/ Factor being investigated	Factors which affect continuing success.
Comparisons	No comparisons.
Length of Study/ Follow-up	12 month follow up.
Outcome measures studied	Factors which affect continuing success at 6 and 12 months.
Results	22 children became dry at the baseline and were not treated with an alarm, and 1 of these relapsed by 12 months. 8 children were lost to follow up after the initial visit and 1 was referred for surgical management. Therefore 96 children were treated with an alarm, 81 of these children became dry for 42 nights. The study showed no stressful event for the child ($p<0.05$), no psychiatric disorder ($p<0.01$), no stress in the family ($p<0.02$), moderate to great parental concern ($p<0.05$) and moderate to great child distress ($p<0.01$) increased the chance of continuing success at 6 months. The study showed at 6 months that children with no adverse events increased failure rate by 5%, family stress increased the risk by 20%, lack of child's distress doubled the risk, and family stress and lack of child's distress quadrupled the risk. The study showed no daytime wetting ($p<0.02$), no urological disorder ($p<0.01$), no psychiatric disorder ($p<0.01$), no developmental disorder ($p<0.01$), parental concern ($p<0.01$) and the child's distress ($p<0.01$) increased the chance of continuing success at 12 months. The study showed at 12 months that for children with no adverse events the risk of failure was 1 in 10, lack of child distress stress increased the risk by 1 quarter, developmental delay increased the risk by 1 third, psychiatric disorder increased the risk by 1 third, having lack of child's distress and developmental delay quadrupled the risk, having lack of child's distress and psychiatric disorder quadrupled the risk, developmental delay and psychiatric disorder increased the risk fivefold, and having all there increased the risk 20-fold.
Safety and adverse effects	None reported
Does the study answer the question?	The study showed no stressful event for the child, no psychiatric disorder, no stress in the family, moderate to great parental concern and moderate to great child distress increased the chance of continuing success at 6 months. The study showed no daytime wetting, no urological disorder, no psychiatric disorder, no developmental disorder, parental concern and the child's distress increased the chance of continuing success at 12 months.
Effect due to factor in study?	The study identified charactersitics which predict continuing success with treatment.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had a mean age of 8.8 years.

Internal Validity

Dische S;Yule W;Corbett J;Hand D;

Childhood nocturnal enuresis: factors associated with outcome of treatment with an enuresis alarm

Ref ID 1472 1983

Study Type Cohort **Funding** Not reported.

Number of participant 245 patients

Inclusion/Exclusion Criteria	Inclusion: wet at least 3 times every week.
Patient Characteristics	Mean age was 7.9 years, age range 4.2 to 14.3 years, ratio of boys:girls was 1.6:1.
Recruitment	Referred to clinician over 5 year period from April 1972 to March 1977 to 4 Community Health special investigation clinics in south-east London UK.
Setting	Southeast London UK.
Interventions/ Test/ Factor being investigated	Factors affecting treatment outcome.
Comparisons	No comparison.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Factors predicting treatment outcome.
Results	Initial interview and examination and the exclusion of urinary infection or other abnormalities by laboratory assessment. Children kept a diary of dry nights for 9 weeks during which parents and children were seen every 2 to 3 weeks and given encouragement and help with family difficulties. The study collected data on demographic data – age, sex, birth order, family size, social class based on the registrar general's classification of the occupation of the male head of household. Unemployed and single-parent families were coded in separate categories. Other characteristics recoreded were parents rating of child's behaviour; teachers rating of child's behaviour; previous treatment for NE; primary or secondary NE; presence of UTI; occurrence of marked daytime wetting; occurrence of soiling; family difficulties; unsatisfactory housing; serious financial hardship; mother working full or part time; history of enuresis in parents or siblings. Children were treated with an alarm. The study showed unsatisfactory housing ($p<0.01$) and family difficulties ($p<0.05$) adversely affect initial success. The failure rate when one of these was present was 12% and if both were present the failure rate increased to 47%. The study showed children with deviant scores on the teacher's rating scale ($p<0.05$) and the presence of family difficulties ($P<0.01$) were related to relapse. The study showed deviant scores on the teacher's rating scale ($p<0.05$) and the presence of family difficulties ($P<0.01$) adversely affect long-term success.
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed unsatisfactory housing and family difficulties adversely affect initial success. The study showed children with deviant scores on the teacher's rating scale and the presence of family difficulties were more likely to relapse. The study showed deviant scores on the teacher's rating scale and the presence of family difficulties adversely affected long-term success.
Effect due to factor in study?	The study identified factors affecting treatment success
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Children had a mean age of 7.9 years

Internal Validity

Daytime functional bladder capacity as a predictor of response to desmopressin in monosymptomatic nocturnal enuresis

Ref ID 4098 1998

Study Type Cohort **Funding** Not reported.

Number of participant	51 patients
Inclusion/Exclusion Criteria	Inclusion: monosymptomatic NE and wet at least 3 times a week.
Patient Characteristics	37 boys and 14 girls, mean age 11 years, and age range 5 to 11 years.
Recruitment	Children presenting to the institutions.
Setting	2 centre in Canada and 1 centre in USA
Interventions/ Test/ Factor being investigated	Factors predicting response to desmopressin.
Comparisons	No comparison.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Factors predicting response to desmopressin.
Results	8 patients were excluded due to insufficient data. 8 patients were excluded due to lack of bladder capacity values. Therefore 35 patients were included in the evaluation. A voiding history was conducted on the number of wet nights per week, nocturia, frequency, urgency dysuria and the presence of daytime wetting; if patients displayed symptoms other than NE they were excluded from the study. The study conducted voiding diaries, daytime functional bladder capacity and urine osmolality. Desmopressin was given over 2 weeks starting at 10 micrograms rising by 10micrograms every 3 days until a response was achieved or 40 micrograms was reached. The study showed daytime functional bladder capacity (p=0.009), maximal functional bladder capacity expressed as a percentage of normal for age (p=0.006) and age (p=0.008) were significant predictors of response to desmopressin. The study showed children who had 70% or more bladder capacity had an 83% chance of success with desmopressin.
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that daytime functional bladder capacity, maximal functional bladder capacity expressed as a percentage of normal for age and age were significant predictors of response to desmopressin.
Effect due to factor in study?	The study identified signficant predictors of response to desmopressin.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had monosymptomatic NE and a mean age of 11 years.
Internal Validity	

Evans JH;Meadow SR;

Desmopressin for bed wetting: length of treatment, vasopressin secretion, and response.[see comment]

Ref ID 1134 1992

Study Type Cohort **Funding** Ferring Pharmaceuticals

Number of participant	55 children: 28 in the 1 month group, and 27 in the 3 month group.
Inclusion/Exclusion Criteria	Inclusion: aged 5 to 16 years, wet at least 2 nights a week, and referred by GP, community medical officer, urologist or paediatrician. Exclusion: taking medication that might cause diuresis (e.g. salbutamol), or UTI in previous 2 weeks.
Patient Characteristics	In the 1 month group: the median age was 10 years, age range 6 to 16 years, 17 out of 28 were male, 19 had previously tried treatment for NE, 15 were wet less than or equal to 2 nights a week, 10 had adverse family or social factors, 9 had a Rutter A2 score of greater than 18, 9 were aged less than 8 years, 9 had adverse housing, 8 had diurnal symptoms, and 1 had allergic rhinitis. In the 3 month group: the median age was 10.8 years, age range 6 to 16 years, 17 out of 27 were male, 19 had previously tried treatment for NE, 17 were wet less than or equal to 2 nights a week, 11 had adverse family or social factors, 8 had a Rutter A2 score of greater than 18, 7 were aged less than 8 years, 6 had adverse housing, 7 had diurnal symptoms, and 1 had allergic rhinitis.
Recruitment	Referred by GP, community medical officer, urologist or paediatrician to enuresis clinic.
Setting	Hospital outpatient department, Leeds.
Interventions/ Test/ Factor being investigated	Comparison of characteristics between responses to desmopressin for children treated with 1 month desmopressin and 3 month desmopressin.
Comparisons	Between treatment lengths and response.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Differences in characteristics of children who responded to desmopressin and children who did not respond to desmopressin.
Results	Children were given 20 micrograms desmopressin rising to 40 micrograms desmopressin if child had any wet nights in first 3 nights of treatment. The study measured response to desmopressin based on treatment length and nocturnal urine volume, nocturnal urine osmolality and nocturnal urine AVP concentration. There were no significant differences between children treated for 1 month and children treated for 3 months in: the proportion of responders during and after treatment and the difference in the number of children who became completely dry. The study showed there were no significant differences between children who responded and children who did not to desmopressin in nocturnal urine volume, nocturnal urine osmolality and nocturnal urine AVP concentration.
Safety and adverse effects	1 child had chest pain and wheezing and stopped treatment, 5 children failed to respond and stopped treatment early.
Does the study answer the question?	The study showed there were no significant differences between children who responded and children who did not to desmopressin in nocturnal urine volume, nocturnal urine osmolality and nocturnal urine AVP concentration. The study showed the length of treatment did no significantly change the response rate.
Effect due to factor in study?	The study showed there were no significant differences between children who responded and children who did not to desmopressin.

Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had an age range 6 to 16 years.

Internal Validity

Kruse S;Hellstrom AL;Hanson E;Hjalmas K;Sillen U;Swedish ESG;

Treatment of primary monosymptomatic nocturnal enuresis with desmopressin: predictive factors

Ref ID 3920 2001

Study Type Cohort **Funding** Ferring Pharmaceuticals, Malmo, Sweden

Number of participant	392 patients with primary nocturnal monosymptomatic enuresis.
Inclusion/Exclusion Criteria	Inclusion: aged 6 to 12 years, primary NE, and at least 10 wet nights in 28 nights.
Patient Characteristics	75% were male,and the age range was 6 to 12 years.
Recruitment	Not reported.
Setting	Multicentre study, Sweden.
Interventions/ Test/ Factor being investigated	Patient characteristics and predictive factors for the outcome of treatment with 20 to 40 micrograms desmopressin.
Comparisons	Between those who responded to treatment with desmopressin and those who didn't.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Response to desmopressin in relation to characteristics.
Results	The following characteristics were recorded: gender, age, heredity, sleep pattern, previous treatments, number of wet episodes during the night, timing of wet episodes, diary of 4 week baseline period including number of wet nights, dose of treatment, number of wet nights in last 4 weeks of treatment. Patients had 6 weeks of 20 to 40 micrograms desmopressin. The response to desmopressin was spilt into 4 categories: no response, partial response (less than 50% reduction), responders (50 to 90% reduction) and full responders (greater than 90% reduction). The study showed there was a significant difference in the response rate to desmopressin by age (responders and full responders were older), the timing of wet episodes (responders wet after midnight, where as non responders wet before and after midnight). Fewer wet nights during observation period had a better response rate to desmopressin, and the frequency of wetting was also significantly different with more frequent being less likely to respond. The study showed there was no difference in the response rate to desmopressin for gender, hereditary and previous treatment.
Safety and adverse effects	None reported.

Does the study answer the question?	The study showed there was a significant difference in the response rate to desmopressin by age (responders and full responders were older), the timing of wet episodes (responders wet after midnight, where as non responders wet before and after midnight). Children with fewer wet nights during observation period had a better response to desmopressin,and the frequency of wetting was also significantly different with more frequently wet children being less likely to respond.
Effect due to factor in study?	The study showed significant predictors for treatment success with desmopressin.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had an age range of 6 to 12 years and monosymptomatic primary NE.

Internal Validity

Kruse S;Hellstrom AL;Hjalmas K;

Daytime bladder dysfunction in therapy-resistant nocturnal enuresis. A pilot study in urotherapy

Ref ID 674 1999

Study Type Cohort **Funding** Not reported.

Number of participant	22 children, 11 in the treatment group and 11 controls.
Inclusion/Exclusion Criteria	Inclusion: aged over 10 years, tried several treatments for NE and with hold pattern daytime Exclusion: no neurological disorder or other disease
Patient Characteristics	For children who were in the treatment group: 8 boys and 3 girls, mean age was 12.8 years, median ages was 12, age range was 10 to 16 years, 6 children had been treated for daytime urge incontinence but for 1 to 5 years had no micturition problems during the day. The mean baseline wetting was 10.5 nights over 2 weeks. Most children had received latest treatment in previous 12 months For children who were in the control group: 6 boys and 5 girls, mean age was 12 years, median ages was 11, age range was 10 to 16 years, 5 children had been treated for daytime urge incontinence. The mean baseline wetting was 8.7 nights over 2 weeks.
Recruitment	Referred to the department for severe therapy-resistant primary NE.
Setting	Sweden
Interventions/ Test/ Factor being investigated	Micturition treatment
Comparisons	Between children treated for micturition problems and those not treated.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Response rates.
Results	For the treatment group: volumes and time of micturitions and fluid intakes were recorded over 1 or 2 days, voided volumes at night were also recorded, if the child was dry the amount voided in the morning was recorded. The child was given information on how the bladder works and was told to void every 2 to 3 hours and drink regularly during the day. After 1 month all children in the treatment group had significantly improved, 1 child was taken to the bathroom at night and 5 had started desmopressin, 1 of which

	became completely dry. After 5 months 4 children had started desmopressin, 1 had dropped out and started acupuncture. In the group without pre-treatment measurements 5 children used the alarm, after 5 months 2 children were still using the alarm and after 12 months no one was using the alarm.
Safety and adverse effects	None reported.
Does the study answer the question?	After 1 month all children treated for micturition were significantly drier.
Effect due to factor in study?	Study suggest micturition increases dryness.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were treatment resistant.
Internal Validity	

Kwak KW;Park KH;

Clinical inconsistency of lower urinary tract symptoms between questionnaire and bladder diary in children with nocturnal enuresis

Ref ID 3921 2008

Study Type Cohort **Funding** Not reported.

Number of participant	108 patients with enuresis.
Inclusion/Exclusion Criteria	Inclusion: wet at least 2 times a week.
Patient Characteristics	80 males and 28 females, mean age 7.2 years, age range 5 to 15 years, and 60% had previous treatment for NE.
Recruitment	Visiting enuresis clinic between Jan 2003 and March 2006.
Setting	Hospital, Korea.
Interventions/ Test/ Factor being investigated	Bladder diaries.
Comparisons	Non validated LUTS questionnaire.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Difference in two methods: 3-day bladder diary and questionnaire.
Results	Non validated LUTS questionnaire completed 1 month before clinic visit, Bladder diary kept for 3 days 1 to 2 weeks after first visit, comparison on classification of NE (monosymptomatic (MNE) or non monosymptomatic (NMNE)), urinary frequency, daytime incontinence and voiding postponement. The study also considered the differences in MVV, AVV, % MVV/EBC, max flow rate and residual urine between monosymptomatic children and non monosymptomatic children as classified by the questionnaire and then by the bladder diaries The study used the Kappa test to compare results of the two methods. The results discrepancies between the classification of NE (kappa test 0.292), and showed there

	was no significant consistency for urinary frequency (kappa test = 0.912). The study showed no consistency on daytime incontinence (kappa test 0.356) and voiding postponement (Kappa test 0.505). For classification of MNE and NMNE by the bladder diaries the study showed the MVV (p = 0.006), AVV (p = 0.001) and % MVV/EBC (p = 0.041) to be statistically different between children with MNE and NMNE, There was no statistical difference in the max flow rate (p = 0.225) and residual urine (p = 0.854) between MNE and NMNE. For classification of MNE and NMNE by the non validated LUTS questionnaire the study showed no statistically significant difference between MNE and NMNE on the MVV (p = 0.559), AVV (p = 0.597) and % MVV/EBC (p = 0.947), the max flow rate (p = 0.122) and residual urine (p = 0.187).
Safety and adverse effects	None reported
Does the study answer the question?	The study showed there were differences in the results of the non validated LUTS questionnaire and the bladder diaries.
Effect due to factor in study?	The study identified differences in information collected from a bladder diary and from a questionnaire.
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Children were treatment resistant and had a mean age of 7.2 years

Internal Validity

McGrath KH;Caldwell PHY;Jones MP;

The frequency of constipation in children with nocturnal enuresis: A comparison with parental reporting

Ref ID 667 2008

Study Type Cohort **Funding** Not reported

Number of participant	277 patients
Inclusion/Exclusion Criteria	Inclusion: referred to clinic by GP or paediatrician between 26 June 2003 and 7 November 2005 for assessment and management of bedwetting.
Patient Characteristics	The mean age was 9.25 years, age range 4.8 to 17.5 years and 65.7% were male.
Recruitment	Referred to clinic by GP or paediatrician between 26 June 2003 and 7 November 2005 for assessment and management of bedwetting, NE clinic, The Children's Hospital, Westmead, Sydney, Australia (tertiary paediatric teaching institution).
Setting	Australia
Interventions/ Test/ Factor being investigated	Constipation is assessed by parental questionnaire and clinician assessment.
Comparisons	Between two assessments.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Differences in two assessments and differences between constipated and non constipated children.

Results	The parental questionnaire was completed at initial presentation prior to seeing the clinician. It contained questions on child's pattern of NE, history of UTIs, fluid intake, bowel habits and parental identification of constipation. The clinician's assessment was by an experienced paediatrician using the parental questionnaire as a prompt to obtain further information and clarification from parent and child, a history of urinary function, bowel habits, fluid and dietary intake and previous treatment for NE. The child was examined including abdominal palpitation. Constipation was defined on the Rome II definition: having more than one of the following – frequency of defecation 3 times a week or less, consistency of stool described as hard (Bristol types 1-3), the presence of straining during defecation Differences in constipated and non constipated children: There was a statistical difference between children who were constipated and children who were not constipated on previous treatment with an alarm (more children who were constipated had tried an alarm). There was a statistical difference between children who were constipated and children who were not constipated on gender, severity of NE – frequency and amount of urine leakage, previous treatment with desmopressin and triclyclics. Comparison of parental questionnaire and clinicians assessment: Of the children parents reported as constipated, 22 out of 39 were found to be constipated by the clinicians and 17 out of 39 were found not to be constipated by the clinician. Of the children parents reported as not constipated 73 out of 231 were found to be constipated by the clinicians and 158 out of 231 were found not to be constipated by the clinician. Differences in individual parameters of two assessments: There was a statistical difference in the reported of soiling in the last 6 months and frequency of defecation between parental questionnaires and clinicians assessment. There was no statistical difference between straining and consistency of stools between parental questionnaires and clinicians assessment.
Safety and adverse effects	None reported
Does the study answer the question?	The study showed children who were constipated were more likely to have tried an alarm. The study showed there was a statistical difference in the reporting of soiling in the last 6 months and frequency of defecation between parental questionnaires and clinicians assessment. There were some differences in the parental diagnosis of constipation and the clinicians.
Effect due to factor in study?	Study considered the difference in reporting of constipation and soiling.
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Set in tertiary care and had a mean age of 9.25 years.

Internal Validity

Persson-Junemann C;Seemann O;Kohrmann KU;Junemann KP;Alken P;

Comparison of urodynamic findings and response to oxybutynin in nocturnal enuresis

Ref ID 1077 1993

Study Type	Cohort	**Funding**	Not reported
Number of participant	63 patients		
Inclusion/Exclusion Criteria	Inclusion: pre-treated persistent NE, and wet at least 4 nights a week. Exclusion: anatomic-urologic defects, overt neurologic disease, or prior infection.		

Patient Characteristics	37 were male and 26 were female. The age range was 6 to 14 years and median was 8.5 years. 59% had diurnal symptoms (frequency, urge) and 14% had occasional daytime wetting.
Recruitment	Not reported, at Department of Urology, Mannheim Hospital, University of Heidelberg, FRG.
Setting	University of Heidelberg, FRG.
Interventions/ Test/ Factor being investigated	Standard urodynamic evaluation and response to treatment with oxybutynin.
Comparisons	No comparison
Length of Study/ Follow-up	No follow up
Outcome measures studied	Differences in urodynamic findings and response to treatment with oxybutynin.
Results	In 10 (16%) children the urodynamic findings were normal without any detectable urinary storage or micturition disorder. In the remaining 53 patients (84%) had findings attributed to an inadequate bladder storage function. 51 children (81%) had reduced maximal bladder capacity, values of less than 50% predicted normal was found in 20 children (32%). 2 children (3%) had reduced bladder capacity which was concomitant with a decreased bladder compliance. 43 children had uninhibited detrusor contractions – 18 children had Grade 1 involuntary contraction (16-50 cm H20); 11 children had Grade 2 involuntary contraction (50-100 cm H20); and 14 children had Grade 3 involuntary contraction (greater than 100 cm H20). In all but 1 child the uninhibited contractions and reduced capacity were coherent. Most children also presented with a low-compliant bladder (mean 77%) the grade-related frequency was reciprocal depending on tendency. All children were treated with oxybutynin. 70% of the original 63 children were either successful or had an improved rate. In the children with normal urodynamic findings 30% of children were either successful or had an improved rate. In children with uninhibited bladder contractions 77% were either successful or had an improved rate. In children with detrusor instability: 78% of children with Grade 1 were either successful or had an improved rate; 9% of children with Grade 2 were either successful or had an improved rate; 64% of children with Grade 3 were either successful or had an improved rate and 76% of all children with reduced bladder capacity were either successful or had an improved rate. There was significant benefit in 84% of children with limited reduction and in 65% of children with more than 50% reduction of the age-corresponding estimate. 41% of children with normal bladder capacity responded to treatment. There was no significant age or gender response to treatment with oxybutynin.
Safety and adverse effects	None reported
Does the study answer the question?	Children with uninhibited bladder contractions, graduation of destrusor instability, reduced bladder capacity and the extent of volume decrease were all more successful on treatment with oxybutynin.
Effect due to factor in study?	Study identified predictors of response to oxybutynin.
Consistency of results with other studies?	No other similar studies.

Directly applicable to guideline population?	Treatment resistant population with a median age of 8.5 years.
Internal Validity	

Redman JF;Seibert JJ;

The uroradiographic evaluation of the enuretic child

Ref ID 1585 1979

Study Type	Cohort	**Funding**	Not reported

Number of participant	138 patients
Inclusion/Exclusion Criteria	#Deleted
Patient Characteristics	Not reported
Recruitment	Referred for NE between July 1972 and July 1977, University of Arkansas college of medicine and Arkansas Children's Hospital
Setting	Arkansas, USA
Interventions/ Test/ Factor being investigated	IVP or cystography
Comparisons	No comparison
Length of Study/ Follow-up	No follow up
Outcome measures studied	Radiographic findings
Results	#Deleted
Safety and adverse effects	None reported
Does the study answer the question?	#Deleted
Effect due to factor in study?	Study identified characterisitcs in a NE population
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Children had an age range of 3 to 8 years
Internal Validity	

Riccabona M;Oswald J;Glauninger P;

Long-term use and tapered dose reduction of intranasal desmopressin in the treatment of enuretic children

Ref ID 776 1998

Study Type	Cohort	**Funding**	Not reported

Number of participant	155 patients
Inclusion/Exclusion Criteria	Inclusion: aged over 5 years, wet at least 3 nights a week, no urological abnormalities on ultrasound, no post-residual urine, negative urine culture, and nocturnal urine volume exceeding their present bladder capacity as recorded on a 3-day/night/frequency/volume chart.
Patient Characteristics	68% were male, 32% were female, mean age was 8 years, and age range was 5 to 19 years. 15% had additional daytime urge symptoms and received oxybutynin before desmopressin therapy. 85% had monosymptomatic NE.
Recruitment	Patients had primary NE.
Setting	Austria.
Interventions/ Test/ Factor being investigated	Desmopressin withdrawal program.
Comparisons	No comparison.
Length of Study/ Follow-up	Median 18 months follow up.
Outcome measures studied	Response to structured withdrawal program from desmopressin.
Results	Children had 20 micrograms intranasal desmopressin titrated to 40 micrograms or 50 micrograms after 2 days if the child did not become dry within 48 hours. This was maintained for 4 to 6 weeks. After 4 weeks of complete dryness the dose was reduced by 10 micrograms and after each additional 4 weeks dry a further 10 micrograms reduction was done. The medication was stopped after 4 weeks dry on 10 micrograms dose. Medication was restarted at the previous dose if a relapse occurred in the reduction phase (relapse was 2 or more wet nights over 2 weeks). Children were also advised to minimize or avoid drinking 2 to 3 hours before bedtime. 113 patients responded to desmopressin. 110 patients achieved complete dryness with no relapses and remained dry without treatment. 11 patients achieved dryness after relapses during or after therapy, 5 had relapses during the reduction phase, 6 after therapy. 11 children improved and had no more than 2 wet nights per week. 22 children did not respond to therapy or improved slightly and had more than 2 wet nights per week. The mean duration of treatment was 28 weeks with a range of 3 months to over 2 years. The mean dosage of desmopressin was 30 micrograms and median follow up was 18 months
Safety and adverse effects	3 children had headaches, and 1 had rhinitis.
Does the study answer the question?	71% of children achieved complete dryness with no relapses and remained dry without treatment with the withdrawal program.
Effect due to factor in study?	Study suggested withdrawal program increased continuing success.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Chidlren had a mean age of 8 years.
Internal Validity	

Schaumburg HL;Rittig S;Djurhuus JC;

No relationship between family history of enuresis and response to desmopressin

Ref ID 4077 2001

Study Type Cohort **Funding** Not reported.

Number of participant	381 patients: 328 with NE and n= 53 controls (no enuresis).
Inclusion/Exclusion Criteria	Inclusion: monosymptomatic NE and had received some type of treatment previously.
Patient Characteristics	NE group: 220 boys and 108 girls. The mean age of the boys was 10 years (age range 5 to 17 years), and the mean age of the girls was 10.5 years (age range 5 to 17 years). Controls: 31 boys and 22 girls. The mean age was 10 years (age range 7 to 13 years). There was no statistically significant difference in the gender differences between the two groups.
Recruitment	Referred by GP to enuresis clinic.
Setting	Enuresis clinic Denmark.
Interventions/ Test/ Factor being investigated	Questionnaire of NE, 20 micrograms intranasal desmopressin for 1 week, 40 micrograms intranasal desmopressin for second week.
Comparisons	Between children with NE and controls (no enuresis).
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Differences in family history of enuresis and response to desmopressin.
Results	Questionnaire - type of NE (primary or secondary – secondary was wetting after a period of at least 6 months dry), family history of NE (1st order relatives were siblings and parents) if a family history was present the duration of NE was specified, and presence of daytime symptoms. Children were described as severe NE if they had at least 3 wet nights a week. There was a statistically significant difference for family history of NE between children with NE and children without NE. 245 out of 328 (75% of children with NE) had a positive family history, compared to 20 out of 53 (38%) of children in the control group ($p<0.001$). The prevalence of first order relatives with a history of NE was higher in patients with NE than the controls. Although patients were referred for monosymptomatic NE 27% indicated additional daytime symptoms. 90% of patients had severe NE, 10% had non severe NE. There was a high prevalence of family history in both these groups. There was no statistically significant difference within or between subgroups regarding gender, monosymptomatic NE and the presence of additional daytime symptoms, primary/secondary EN or a positive family history of NE (first order or other relative). All patients with NE had treatment with desmopressin. There was no statistical differences in the rates of response between children with severe NE and children with non-severe NE or in the prevalence of a positive family history.
Safety and adverse effects	None reported.
Does the study answer the question?	There was a statistically significant difference for family history of NE between children with NE and children without NE. There was no statistical differences in the rates of response to desmopressin between children with severe NE and children with non-severe NE or in the prevalence of a positive family history.
Effect due to factor in study?	Study identified differences in charateristics of patients with NE and without NE.

Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had an age range of 5 to 17 years.

Internal Validity

Siegel S;Rawitt L;Sokoloff B;Siegel B;

Relationship of allergy, enuresis, and urinary infection in children 4 to 7 years of age

Ref ID 1689 1976

Study Type Cohort **Funding** Not reported.

Number of participant	234 patients
Inclusion/Exclusion Criteria	Inclusion: 4 to 7 years, middle to upper middle class, Caucasian Exclusion: children with occasional NE and occasional day wetting
Patient Characteristics	75% were aged 4 to 5 years, 25 % were aged 6 to 7 years
Recruitment	Not reported
Setting	USA
Interventions/ Test/ Factor being investigated	Rate of NE in children treated for UTI and children with allergy
Comparisons	No comparison
Length of Study/ Follow-up	No follow up
Outcome measures studied	Number of children with persistent NE (wetting every week)
Results	Group 1 included 50 children previous treated for UTI and 55 healthy controls matched for age and sex. Group 2 included 69 children with allergies, with nasal bronchial hypersensitivity to respiratory allergens severe enough to warrant avoidance, medication and desensitization and 60 controls without allergies matched for age and sex. There was no statistical difference between the number of children with persistent NE (night wetting every week) who had previously been treated for UTI and controls (20% in each group). There was no statistical difference between the number of children with persistent NE (night wetting every week) who had allergies and controls (13% in allergy group and 23% in control group).
Safety and adverse effects	None reported.
Does the study answer the question?	There was no statistical difference between the number of children with persistent NE (night wetting every week) who had previously been treated for UTI and controls (20% in each group). There was no statistical difference between the number of children with persistent NE (night wetting every week) who had allergies and controls (13% in allergy group and 23% in control group).
Effect due to factor in study?	Study did not identiiy any relationship between respiratory allergy, enuresis, and urinary infection.

Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Chidlren had an age range of 4 to 7 years.

Internal Validity

Sujka SK;Piedmonte MR;Greenfield SP;

Enuresis and the voiding cystourethrogram: a re-evaluation.[see comment]

Ref ID 1152 1991

Study Type	Cohort	**Funding**	Grant from the National Cancer Institute

Number of participant	86 patients in results (132 originally)
Inclusion/Exclusion Criteria	Inclusion: NE, and patients give full historical details (see result section) Exclusion: UTI
Patient Characteristics	46 out of 86 were male. 13 patients had reflux and 70 did not have reflux In the reflux group: the mean age was 6.6 years, 23% were male, 62% had daytime wetting, 46% had urgency, 31% had frequency, and 82% had secondary NE. In the non-reflux group: the mean age was 7.45 years, 61% were male, 54% had daytime wetting, 24% had urgency, 24% had frequency, and 23% had secondary NE.
Recruitment	Patients seen between July 1984 and July 1986.
Setting	Department of Urology, Buffalo, USA
Interventions/ Test/ Factor being investigated	Historical details, urine cultures, a contract voiding cystourethrogram (VCUG), upper urinary tract studies (intravenous pyelogram (IVP) or renal ultrasound).
Comparisons	No comparisons.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Presence of symptoms indicating a greater likelihood of VUR.
Results	Historical details: age of presentation, daytime wetting, urgency, frequency, UTI, primary or secondary NE. Urine cultures, a contract voiding cystourethrogram (VCUG), upper urinary tract studies (intravenous pyelogram (IVP) or renal ultrasound). The study conducted a linear logistic regression model to investigate if the presence of symptoms indicating a greater likelihood of VUR. Historical details: In the reflux group the mean age was 6.6 years, 23% were male, 62% had daytime wetting, 46% had urgency, 31% had frequency, and 82% had secondary NE. In the non-reflux group the mean age was 7.45 years, 61% were male, 54% had daytime wetting, 24% had urgency, 24% had frequency, and 23% had secondary NE. Results of logistic regression analysis: daytime wetting had a regression coefficient of 0.2255 and p value of 0.7298; urgency had a regression coefficient of 1.1794 and p value of 0.1708; frequency had a regression coefficient of -0.5778 and p value of 0.5306; secondary NE had a regression coefficient of 0.6379 and p value of 0.3221 Results of 17 refluxing ureters in 13 patients with reflux and no history of UTI: grade I reflux there were 7 refluxing ureters, 1 with scarring and 0 had undergone surgery; grade II reflux there were 5 refluxing ureters, 0 with scarring and 0 had undergone

	surgery; grade III reflux there were 3 refluxing ureters, 0 with scarring and 0 had undergone surgery; grade IV reflux there were 4 refluxing ureters, 2 with scarring and 2 had undergone surgery; grade V reflux there were 0 refluxing ureters, 0 with scarring and 0 had undergone surgery.
Safety and adverse effects	None reported
Does the study answer the question?	The study showed no historical details could predict if children had VUR. The study showed out of 13 patients with reflux there were 7 grade I refluxing ureters and 12 greater than or equal to grade II refluxing ureters.
Effect due to factor in study?	Study did not identify any differences.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	The mean age of children with reflux was 6.6 years and the mean age of chidlren without reflux 7.45 years
Internal Validity	

Tanaka Y;Kawauchi A;Yoneda K;Naitoh Y;Yamao Y;Iwasaki H;Mizutani Y;Miki T;

Vesicoureteral reflux detected among patients with nocturnal enuresis

Ref ID 443 2003

Study Type Cohort **Funding** Not reported

Number of participant	1088 patients had voiding cystourethrography (VCUG) after presenting with nocturnal enuresis.
Inclusion/Exclusion Criteria	Patients with nocturnal enuresis.
Patient Characteristics	Mean age was 9.9 years. 738 were male and 350 were female. 627 had monosymptomatic NE and 461 had day time symptoms. 70 children had reflux, 36 of which had monosymptomatic NE and 34 had day time symptoms. Characteristics of children with reflux: the mean age of children with reflux was found was 8.8 (sd 3.1) years, 71% were male, 7% had pyuria, 1% had a renal (kidney) scar, and 75% had over active bladder.
Recruitment	Visited clinic with NE and underwent voiding cystourethrography (VCUG), Department of urology, Kyoto Prefectural University of Medicine
Setting	Japan.
Interventions/ Test/ Factor being investigated	Clinical history of NE, family history, check for exsisting diseases, urinary analysis, urological disease, voiding cystourethrography (VCUG), cystometry, intravenous pyelography or renal ultrasonography, radiography of lumbar vertebrae to assess occult spina bifida.
Comparisons	No comparison
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Clinical difference in children with and without reflux
Results	Clinical history of NE, family history, check for exsisting diseases, urinary analysis, urological disease, voiding cystourethrography (VCUG), cystometry, intravenous pyelography or renal ultrasonography, radiography of lumbar vertebrae to assess occult spina bifida. Children were treated with anticholinergics drugs (oxybutynin chloride and propiverine hydrocholoride)

70 children had reflux, 36 of whom had monosymptomatic NE and 34 of whom had day time symptoms.

Clinical characteristics of children with reflux: the mean age of children with reflux was 8.8 (sd 3.1) years, 71% were male, 7% had pyuria, 1% had a renal (kidney) scar, and 75% had an over active bladder.

A total of 86 ureters had reflux: 25 (29%) were grade I, 50 (58%) were grade II, 11 (13%) were grade III, 0 (0%) were grade IV and 0 (0%) were grade V.

Resolution of reflux in patients follow-up for 2 years or more
4 out of 6 (66%) with grade I reflux had resolved; 11 out of 20 (55%) with grade II reflux had resolved; 3 out of 6 (50%) with grade III reflux had resolved.

There was no statistically significant difference in the number of children with improved NE 2 years after the first visit between children with resolution of reflux and children without resolution of reflux. 61% of children with resolution of reflux had improved NE compared to 36% of patients without resolution of reflux.

The study compared characteristics of patients with reflux to patients without reflux. Having a positive history of NE in siblings and frequency were both statistically more common in children with reflux. The following showed no statistical difference: sex, age, secondary NE, frequency of NE per week, positive history of NE in parents, daytime incontinence, UTI and occult spina bifida.

Safety and adverse effects None reported

Does the study answer the question? The study showed having a positive history of NE in siblings and frequency were both statistically more common in children with reflux.

Effect due to factor in study? Study identified differences between the two groups.

Consistency of results with other studies? No other similar studies.

Directly applicable to guideline population? Children had a mean age of 9.9 years.

Internal Validity

van dM;

Urodynamics in enuretic children

Ref ID 1120 1992

Study Type Cohort **Funding** Not reported

Number of participant 124 patients

Inclusion/Exclusion Criteria Included children with enuresis.

Patient Characteristics 50 children were aged 5 to 7 years, 37 patients were aged 8 to 10 years, 22 patients were aged 11 to 13 years and 15 patients were aged 14 to 18 years. Treatment resistant patients.

Recruitment Not reported

Setting Netherlands

Interventions/ Test/ Factor being investigated	Renography
Comparisons	No comparison
Length of Study/ Follow-up	No follow up
Outcome measures studied	Urodynamic findings
Results	Children were examined under physiologic conditions 61% of children had micturition 55% had decreased bladder capacity 22% had abnormal urine flow pattern 7% had anatomical obstruction 14% had functional disturbance 4% had changeable urine flow patterns 23% had renography 9.6% had had vesico-renal reflux 1.5% had significant dilated renal pelvis 7% had slight non-obstructive dilated pelvis 1.7% had parenchymal kidney damage (3 out of 5 of these children also had vesico-renal reflux) 0.8% had had afunctional kidney 2.4% had other clinical factors which were not important.
Safety and adverse effects	None reported
Does the study answer the question?	The study aim was to identify abnormalities probably related to NE.
Effect due to factor in study?	The study identified charateristics of an NE population.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Treatment resistant populatiuon with an age range of 5 to 18 years.

Internal Validity

Yeung CK;Sreedhar B;Leung VT;Metreweli C;

Ultrasound bladder measurements in patients with primary nocturnal enuresis: a urodynamic and treatment outcome correlation

Ref ID 4091 2004

Study Type Cohort **Funding** Not reported.

Number of participant	514 patients
Inclusion/Exclusion Criteria	Inclusion: aged 5 to 18 years and monosymptomatic primary NE.
Patient Characteristics	Mean age 11.2 years.
Recruitment	Enuresis clinic from 1998 to 2002.
Setting	Hong Kong

Interventions/ Test/ Factor being investigated	Bladder wall thickness and bladder volume and their correlations to response to desmopressin.
Comparisons	No comparison.
Length of Study/ Follow-up	No follow up
Outcome measures studied	Relationship between parameters (bladder wall thickness and bladder volume) and response to desmopressin.
Results	339 normal age matched children without urinary symptoms referred for other minor surgery. Children under went scans with patient supine using ATL 500 and ESAOTE Technos ultra sound unit with 5 MHz frequency probe 20 minutes after drinking as much as possible. Renal volumes were also calculated. The study showed children with a thicker bladder wall were less likely to respond to desmopressin. The study showed children with a larger bladder volume were more likely to respond to desmopressin. Children who became completely dry on desmopressin had a mean bladder wall thickness of 0.3633 (sd 0.098), children who had a good response (greater than 90% reduction in wet nights compared with the baseline)had 0.3763 (sd 0.10), partial response (greater than 50% but less than 90% reduction in wet nights) 0.4153 (sd 0.14), no response (no effect or less than 50% reduction0.4143 (sd 0.15). The overall mean BT was 0.3953 (sd 0.13). Children who became completely dry on desmopressin had a mean bladder volume of 636 (sd 232.6), children who had a good response had 564 (sd 264), partial response 527.96 (sd 273.5), and no response 454 (sd 275.57). The overall mean BVI was 535 (sd 261.27).
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed children with a thicker bladder wall were less likely to respond to desmopressin. The study showed children with a larger bladder volume were more likely to respond to desmopressin.
Effect due to factor in study?	Study showed children with a thicker bladder wall were less likely to respond to desmopressin. The study showed children with a larger bladder volume were more likely to respond to desmopressin.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had monosymptomatic NE and had a mean age of 11.2 years.

Internal Validity

Zink S;Freitag CM;von G;

Behavioral Comorbidity Differs in Subtypes of Enuresis and Urinary Incontinence

Ref ID 665 2008

Study Type Cohort **Funding** Not reported

Number of participant	97 patients
Inclusion/Exclusion Criteria	Inclusion: Referred to specialist outpatient clinic for elimination of disorders between January 2004 and July 2006 Exclusion: organic forms of urinary incontinence.

Patient Characteristics	45 children had monosymptomatic NE (MNE) and 52 children had non monosymptomatic NE (NMNE).
Recruitment	Referred for elimination disorders to Department of Child and Adolescent Psychiatry.
Setting	Saarland University Hospital, Germany
Interventions/ Test/ Factor being investigated	Psychological and radiological examination.
Comparisons	Between monosymptomatic (MNE) and non monosymptomatic (NMNE) children.
Length of Study/ Follow-up	Not reported
Outcome measures studied	Differences in CBCL score, ICD-10 score, uroflow, ultrasound residual urine,and bladder wall thickness.
Results	The study conducted: a detailed history, pediatric examination (height, weight, head circumference, examination of chest organs, ears, nose, throat, blood pressure, abdomen, neurological investigation and genital examination), 24 to 48 hour voiding protocols, sonography (kidneys, urinary tract, bladder wall thickness, residual urine, rectal diameter), uroflowmetry. The ICD-10 score was based on a standardised mental status examination (Clinical Assessment Scale of Child and Adolescent Psychopathology-D6) and mutual consensus conferences. CBCL questionnaire which consisted of 113 problem items, 3 aspects – internalizing problem score (withdrawal, somatic complaints, anxiety, depression) externalizing problem score (delinquent and aggressive behaviour) and total problem score (sum of all behaviour problems). A problem score of greater than 63 was the 90th percentile and used for diagnosis. Statistically significant difference for having more than 5 ml residual urine (more common in NMNE), mean number of mm bladder wall thickness (thicker in NMNE). The following results showed no statistically significant difference between children with MNE and children with NMNE; on the CBCL questionnaire the number of patients internalizing T value greater than 63, the number of patients externalizing T value greater than 63, the number of patients with total T value greater than 63; on the ICD-10 score the number of patients externalising disorder, the number of patients with internalising disorder, the number of patients with other disorder, the number of patients with at least 1 psychiatric diagnosis excluding encopresis, the number of patients with encopresis; on the uroflow test the number of patients with pathological, the mean ml volume, the mean ml/sec flow; on ultrasound the mean ml volume of residual urine and on the bladder wall thickening the number of children with greater than 2.5mm
Safety and adverse effects	None reported
Does the study answer the question?	The study showed children with NMNE were more likely to have more than 5 ml residual urine and a higher mean number of mm bladder wall thickness.
Effect due to factor in study?	The study showed children with NMNE were more likely to have more than 5 ml residual urine and a higher mean number of mm bladder wall thickness.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	No age range given.
Internal Validity	

Grading: 2-	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

Fielding D;

Factors associated with drop-out, relapse and failure in the conditioning treatment of nocturnal enuresis

Ref ID 3287 1985

Study Type Cohort **Funding** Not reported.

Number of participant	97 patients: 46 with night and day time wetting and 51 with night time only wetting.
Inclusion/Exclusion Criteria	Inclusion: aged 5 to 15 years, no UTI, showed no evidence of organic pathology and had not been treated with the previous 12 months. Nocturnally enuretic only – child must have displayed no day time wetting after the age of 4 years. Diurnal enuresis was defined as persistent daytime wetting in the absence of organic lesion after the age of 5 years with a wetting frequency of at least once a week. The extent of wetting ranged from damp underclothes to more obvious voiding causing the wetting of top clothes.
Patient Characteristics	Not reported.
Recruitment	Referred to the two specialist clinics set up for the trial Liverpool UK.
Setting	Liverpool UK.
Interventions/ Test/ Factor being investigated	30 variables to predict treatment outcome.
Comparisons	No comparison.
Length of Study/ Follow-up	12 month follow up.
Outcome measures studied	30 variables to predict treatment outcome
Results	Children with daytime wetting were not included in the investigation Extensive interview – history and current status of enuresis, family history of enuresis, social background, occurrence of other behavioural problems. Parents were asked to keep a 4 week record of wet and dry days before treatment began. At the second appointment a water load test was conducted to assess maximum functional bladder capacity. Patients were randomly assigned to retention control training with an alarm or to alarm only therapy. 30 variables were derived from 3 pre-treatment assessment measures – interview, baseline record of wetting-frequency, and clinic measurement of bladder capacity. Factors to predict treatment outcome: 52 children had treatment, 17 children did not become dry after 14 weeks treatment with the alarm. Three variables were associated with treatment failure: frequency of micturition ($p<0.01$), urgency of miturition ($p<0.05$) and previous experience of alarm treatment ($p<0.02$). Neither small pre-treatment functional bladder capacity , behavioural deviance score or severity of night time wetting were related to treatment failure. Factors to predict relapse: 18 out of 34 children had relapsed by 12 months after treatment with the alarm. Many however had subsequently become dry following re-treatment. None of the 30 variables were associated with relapse.
Safety and adverse effects	None reported.

Does the study answer the question?	Three variables were associated with treatment failure: frequency of micturition, urgency of miturition and previous experience of alarm treatment. None of the 30 variables were associated with relapse.
Effect due to factor in study?	Study identified variables associated with treatment failures
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Children had an age range of 5 to 15 years
Internal Validity	Not addressed

Houts AC;Peterson JK;Liebert RM;

The effect of prior imipramine treatment on the results of conditioning therapy in children with enuresis

Ref ID 1411 1984

Study Type Cohort **Funding** Not reported.

Number of participant	57 patients
Inclusion/Exclusion Criteria	Inclusion: lifelong history of NE
Patient Characteristics	45 males and 12 females. The mean age for males was 7.97 (SD 2.16) years, the mean age for females was 8.13 (sd 2.04) years, and the majority wet the bed every night. All had consulted a family physician about NE, and 16% had undergone at least 1 major urological examination. 39% had been treated with clinical trial of imipramine in the previous year and had failed to correct the problem.
Recruitment	Not reported.
Setting	USA.
Interventions/ Test/ Factor being investigated	Factors associated with relapse after alarm treatment: age, gender family history, length of treatment, and previous treatment with imipramine.
Comparisons	No comparison.
Length of Study/ Follow-up	1 year follow up.
Outcome measures studied	Factors associated with relapse.
Results	Treatment success was defined as 14 consecutive dry nights at the end of 8 to 12 weeks of treatment and still dry at follow up interviews (at 6 and 12 months). Relapse was described as 1 wet night per 2 weeks. The study reported the majority of relapses happened by 6 months. The study showed the following factors were significantly associated with relapse: prior treatment with imipramine. The study showed the following factors were not significantly associated with relapse: age, gender family history, and length of treatment. The study went on to examine the relationship between prior treatment with imipramine and with relapse. The study suggested severity of NE could be a factor. However there was no significant difference in the mean number of wet nights, the longest reported period of dryness and initial severity of bed wetting between children

who relapsed and those who remained dry.

Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that prior treatment with imipramine was significantly associated with relapse.
Effect due to factor in study?	Study identified factors associated with relapse.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Males had a mean age of 7.97 years and females had a mean age of 8.13 years.

Internal Validity

Jensen IN;Kristensen G;

Alarm treatment: analyses of response and relapse

Ref ID 3918 1999

Study Type Cohort **Funding** Not reported.

Number of participant	237 patients
Inclusion/Exclusion Criteria	Inclusion: aged 5 to 19 years, no daytime urination problems, no other disease of the urinary tract, at least 3 wet nights per week, and personal and parental motivation to solve the problem together.
Patient Characteristics	Aged 5 to 19 years.
Recruitment	Not reported.
Setting	Denmark.
Interventions/ Test/ Factor being investigated	4 variables to predict response to alarm treatment.
Comparisons	No comparison.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Response to alarm treatment.
Results	The study considered: how often the child was wet before treatment, how often the child was wet after treatment, did the child become completely dry during treatment, was the child dry 1 year after treatment The study stated the patients with the highest number of wet nights were more successful than those with fewer wet nights. The study showed age and gender impact on treatment response. The study stated girls had a higher number of wet nights and therefore have a higher probability of being cured by an alarm. The study reported the number of wet nights rises until the child is 10 years old, while the number of children with NE declines between 6 and 10 years old. However the frequency of wet nights for the remaining age group increases, the authors state this could be because spontaneous remission is more frequent for children with a lower number of wet nights or secondary NE may also lead to an increased frequency of wet nights.

Safety and adverse effects	None reported.
Does the study answer the question?	The study stated the patients with the highest number of wet nights were more successful than those with fewer wet nights. The study showed age and gender impact on treatment response.
Effect due to factor in study?	Study identified factors predicting treatment response.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had an age range of 5 to 19 years.

Internal Validity

Nappo S;Del G;Chiozza ML;Biraghi M;Ferrara P;Caione P;

Nocturnal enuresis in the adolescent: a neglected problem

Ref ID 448 2002

Study Type Cohort **Funding** Not reported.

Number of participant	107 patients
Inclusion/Exclusion Criteria	Inclusion: wet at least 1 night a month in previous 6 months, pubertal stage >2 using tanner classification, aged over 13 years, and no neurological disease or known renal or urinary tract disease.
Patient Characteristics	63 males, 44 females, mean age 15.3 years. 74% had primary NE, 71% had monosymptomatic NE, 37% were first born, and 75% were only child.
Recruitment	From 7 centres in Northern and Southern Italy.
Setting	Centres in Northern and Southern Italy.
Interventions/ Test/ Factor being investigated	Questionnaire to inform treatment.
Comparisons	No comparisons.
Length of Study/ Follow-up	Not reported.
Outcome measures studied	Patient characteristics and response to desmopressin.
Results	A questionnaire based on history, results of physical and diagnostic examinations and therapy. History – family and personal with attention to pregnancy, delivery and birth weight; neonatal period, age of requirement and attainment of urinary and faecal control, coexistent pathologies, occurrence of allergies, and surgery and stressful events. Characteristics of NE – primary or secondary, monosymptomatic or symptomatic, severity of bedwetting, presence of obstipation or encopresis, UTIs, sleep characteristics, previous examinations and therapies, day time symptoms (occurrence of frequency – more than 7 voids/day, urgency, urge incontinence, and / or holding manoeuvres). Physical examination – weight, height, arterial BP, assessment of purbertal stage, inspection of abdomen, external genitalia, lower legs and lumbosacral regions, tests for glucose, bacteria, protein and blood cells in urine, urine cluture, serum glucose, creatinine and electolytes, renal and bladder ultrasonography and uroflowmetry.

Further examination (cystography and urodynamics) were undertaken in selected patients with daytime symptoms.

The study showed statistical differences:
Monosymptomatic NE was significantly more frequent in males than females. NMNE was more frequent in females regardless of age.Females were more likely to have UTI.

Non statistical differences:
74% had primary NE, 26% had secondary NE. 80% of males had primary NE and 64% of females had primary NE.
71% had monosymptomatic NE, 29% had symptomatic NE
There was no difference in family history of NE according to age, gender, types of NE. 37% of patients were first born, 28% second born, 75% were an only child, 2.8% were adopted
The mean neonatal weight was 3.45kg, range 2.1 to 4.7 kg, two patients were born at less than 2.5kg, 9 patients were born at less than 38 weeks all had primary NE
17 patients reported major stressful event, this was not related to the type of NE
29.9% had undergone minor surgery, 5.6% had eating disorders
12.1% had UTIs, 20% in MNE and 42% in NMNE (not statistically different)
Ostipation was found in 34% of females and 17% of males (54% with NMNE and 20% with MNE)
NE was severe (greater than 3 wet nights a week) in 80% of patients 45% were wet every night (no relation to age, gender or type of NE)
Previous treatment: 20% had never sought medical help (no difference in age, gender or severity) 39% had seen paediatricians, 24% had seen psychiatrists, 17% had seen GPs and 15% seen urologists, 3% had seen gynaecologists, also sees were andrology, ephrology or alternative medicine specialists
40% had never received previous treatment, 52.3% had tried oral desmopressin – 79% had responded with 1 patient having a headache. The patients with symptomatic NE were treated with anticholinergics (8 patients) or anticholinergics and oxybutynin (5 patients) or bladder training and biofeedback (4 patients). 8 patients who had not responded to desmopressin were treated with an alarm which was not tolerated by 2. 3% of patients refused all treatment or were not compliant with treatment.

Response to desmopressin:
There was no statistically significant difference in the following variables between those who responded to desmopressin and those who did not: gender, age, family history, frequency of NE (number of wet nights per week)

Safety and adverse effects

None reported.

Does the study answer the question?

The study considered the characteristics as shown in the results section. There was no statistically significant difference in the following variables between those who responded to desmopressin and those who did not: gender, age, family history, frequency of NE (number of wet nights per week).

Effect due to factor in study?

Uncertain.

Consistency of results with other studies?

No other similar studies.

Directly applicable to guideline population?

Children had a mean age of 15.3 years.

Internal Validity

O'Regan S;Yazbeck S;Hamberger B;Schick E;

Constipation a commonly unrecognized cause of enuresis

Ref ID 3940 1986

Study Type Cohort **Funding** Not reported.

Number of participant	29 patients
Inclusion/Exclusion Criteria	Patients were referred for assessment or to eliminate renal pathologic conditions. Constipation was described as – more than 72 hours between bowel movements, presence of overflow incontinence (encopresis), passage of small, hard, scibalous stools with intermittent passage of large stools, poor emptying and dilation of rectal ampulla after defecations determined by rectal examination and grossly decreased level of perception and increased tolerance to balloon insufflation during rectal manometry combined with any element of the four alone.
Patient Characteristics	Not reported.
Recruitment	Referred for assessment or to eliminate renal pathologic conditions.
Setting	University of Montreal, Canada.
Interventions/ Test/ Factor being investigated	Assessment and treatment of constipation.
Comparisons	No comparison.
Length of Study/ Follow-up	9.2 months follow up.
Outcome measures studied	Becoming dry.
Results	25 out of 29 patients had been referred for assessment and treatment of enuresis, 4 had severe functional constipation in the absences of urinary symptoms. 22 out of 25 with enuresis children had a history of constipation. The children underwent urodynamic studies to assess for bladder instability. The children were treated with phosphate enemas. All patients had bladder instability identified by either the presence of uninhibited contractions of the detrusor during the filling phase of the bladder with an amplitude equal or greater than 15 cm H2O or the occurrence of destrusor contraction at the end of or after urinary flow. The mean response time to treatment of NE was 16 (sd 10) days with a range of 3 days to 6 weeks prior to resolution. At follow up 5 out of 7 males had no NE, 2 out of 7 had partial response or wet once a week (from a baseline of 7 nights a week). 9 out of 10 girls had no NE, and 1 out of 10 had partial response or wet once a week (from a baseline of 7 nights a week). 5 children failed to undergo therapy, 1 was treated with imipramine and had a complete response, and 4 children continued to have NE.
Safety and adverse effects	None reported.
Does the study answer the question?	All children who were treated for constipation initially became dry, there were some relapses at follow up. The authors said the study “strongly implicated unrecognized rectal distention as an atiologic facto of enuresis.
Effect due to factor in study?	Study showed treating constipation can increase dryness.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Very specialist referral group, unclear patient charactieristics.
Internal Validity	

Ref ID 817 2005

Study Type Cohort **Funding** Not reported

Number of participant	170 patients in total; 123 patients had primary nocturnal enuresis (PNE) and 47 had secondary nocturnal enuresis (SNE).
Inclusion/Exclusion Criteria	Inclusion: aged of 3.5 years, wet at least 1 night a month, primary NE (PNE) was children who had never achieved a period of night time dryness of over 6 consecutive months; or secondary NE (SNE) was described as the child having had a period of night time dryness of over 6 consecutive months Exclusion: parent or guardian did not know if the child had experience a period of dryness of at least 6 months, structural abnormality of bladder or urethra, major neurologic problem, or morbid obesity.
Patient Characteristics	103 were male, 67 were female, the mean age for children with PNE was 8.05 (sd 2.96), for SNE was 8.12 (sd 3.78)
Recruitment	Attended pediatric urology voiding dysfunction clinic, Health Sciences Centre
Setting	University of Oklahoma, USA
Interventions/ Test/ Factor being investigated	Comparison of patient characteristics for PNE and SNE
Comparisons	No comparison
Length of Study/ Follow-up	No follow up
Outcome measures studied	Differences in patient characteristics of children with PNE or SNE
Results	Questionnaire considering: age and gender, frequency of voiding, nocturia, urgency, squatting behaviour for girls, daytime wetting, UTI, constipation, ADHD, VUR, uroflow and post void residual There was a statistically significant difference between PNE and SNE for constipation: In PNE 74.59% had constipation compared to 57.54% in SNE (p = 0.394; OR 2.17, 95% CI 1.07, 4.41) There was no statistically significant difference between PNE and SNE for: Male gender: In PNE 59.35% compared to 63.93% in SNE (p = 0.7259) Age when voiding on own: In PNE 2.35 (sd 0.71) years compared to 2.13 (sd 0.61) years in SNE (p = 0.0.538) Age when assessed: In PNE 8.05 (sd 2.96) years compared to 8.12 (sd 3.78) years in SNE (p = 0.0.9024) Infrequent voiding: In PNE 14% compared to 17% in SNE (p = 0.6275) Normal frequency: In PNE 45% compared to 48% in SNE (p = 0.7318) Frequent voiding: In PNE 41% compared to 35% in SNE (p = 0.4825) Nocturia: In PNE 25% compared to 22% in SNE (p = 0.6906) Urgency: In PNE 85% compared to 77% in SNE (p = 0.1791) Squatting behaviour for girls: In PNE 36% compared to 38% in SNE (p = 0.8231) Daytime wetting: In PNE 86% compared to 79% in SNE (p = 0.2468) UTI: In PNE 57.72% compared to 65.96% in SNE (p = 0.3832) ADHD: In PNE 18.03% compared to 15.22% in SNE (p = 0.8199) VUR: In PNE 36.73% compared to 17.65% in SNE (p = 0.2273) Normal uroflow: In PNE 63.72% compared to 60.98% in SNE (p = 0.8506) Tower: In PNE 0.88% compared to 4.88% in SNE (p = 0.1731) Interrupter: In PNE 19.47% compared to 17.07% in SNE (p = 0.8193) Obstructive: In PNE 8.13% compared to 8.51% in SNE (p = 1.000) Postvoid residual: In PNE 39.47% compared to 38.30% in SNE (p = 1.0)
Safety and adverse effects	None reported

Does the study answer the question?	The authors reported the only significant difference between children with PNE and SNE was constipation with more children with SNE having constipation
Effect due to factor in study?	Study identified a significant difference between patients with primary and secondary NE
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Mean age 8.05 and 8.12 years

Internal Validity

Van Hoecke E;Baeyens D;Vanden B;Hoebeke P;Vande W;

Early detection of psychological problems in a population of children with enuresis: construction and validation of the Short Screening Instrument for Psychological Problems in Enuresis

Ref ID 86 2007

Study Type Cohort **Funding** Not reported.

Number of participant	Phase I (construction of the SSIPPE): Sample 1, n=261. n=141 patients from previous psychological/emotional problems prevalence studies and 120 from ADHD prevalence studies. Sample 1A (emotional problems): n=63 children. Sample 1B (ADHD): n=48. Phase II (validation of SSIPPE): Sample 2 (newly admitted): n=109.
Inclusion/Exclusion Criteria	Phase II: exclusion: children with anatomical or neurological abnormalities, metnal retardation or chronic diseases.
Patient Characteristics	Aged 6 to 12 years old. Participants had monosymptomatic and non-monosymptomatic nocturnal enuresis diagnosed in a tertiary care setting. The participants had taken part in prevalence studies on psychological/emotional problems (141 patients) and ADHD (120 patients) in enuresis. Sample 1A (63 patients) had enuresis with a clinical/subclinical score on the internalising scale of the CBCL. Sample 1B (48 patients) with diagnosis of ADHD on the DBDRS and the Diagnostic interview schedule for children, parent version. Phase II (validation of SSIPPE): 109 children (76 boys and 33 girls) with a mean age of 8.5 years (s.d. 2.4).
Recruitment	Validation participants were newly admitted to hospital.
Setting	Pediatric Uro/Nephrologic centre (Ghent Uni hosp).
Interventions/ Test/ Factor being investigated	Psychological assessments.
Comparisons	No comparisons.
Length of Study/ Follow-up	No follow-up.
Outcome measures studied	Phase I: emotional problems -31 items of internalising scale of the CBCL. ADHD based on the DBDRS -18 items of the inattention and hyperactivity/impulsivity scales used to find highest loading items for inclusion in SSIPPE.Phase II:sensitivity/specificity
Results	Phase I: Highest loading items of internalising scale of CBCL and ADHD scales of DBDRS on prinicpal factor analysis: Feels others reacting negatively: 0.74 (anxious/depressed) - CBCL Feels worthless: 0.65 (anxious/depressed) - CBCL

Unhappy: 0.65 (anxious/depressed) - CBCL
Lacks energy: 0.69 (withdrawn) - CBCL
Nausea: 0.78 (physical complaints) - CBCL
Headaches: 0.73 (physical complaints) - CBCL
Stomach problems: 0.72 (physical complaints) - CBCL
Insufficient attention: 0.82 (inattention) - DBDRS
Difficulty organising tasks: 0.82 (inattention) - DBDRS
Forgetful in daily tasks: 0.81 (inattention) - DBDRS
Talks continuously: 0.79 (hyperactivity/impulsivity) - DBDRS
Busy: 0.79 (hyperactivity/impulsivity) - DBDRS
Running or climbing: 0.75 (hyperactivity/impusivity) - DBDRS

Phase II: Prediction of CBCL internalising symptoms - sensitivity: 0.75, specificity: 0.91.
DBDRS - inattention sensitivity: 0.29, specificity: 0.99; hyperactivity/impulsivity sensitivity: 0.36, specificity: 0.99.

Safety and adverse effects

None reported.

Does the study answer the question?

ROC curve analysis showed classification accuracy of 88% (considered good). Showed that the 3 SSIPPE subscales had an excellent specificity, leading to few false-negative results and low sensitivity of inattention and hyperactivity/impulsivity leading to higher number of false-positive results.

The authors concluded that the SSIPPE was a time efficient and cost-effective first screening of psychological problems and gives an indication of whether a full psychiatric /psychological screening is necessary.

Effect due to factor in study?

Consistency of results with other studies?

No other similar studies.

Directly applicable to guideline population?

Aged 6 to 12 years.

Internal Validity

Van Hoecke E;Hoebeke P;Braet C;Walle JV;

An assessment of internalizing problems in children with enuresis

Ref ID 4083 2004

Study Type Cohort **Funding** Not reported.

Number of participant

84 patients with enuresis and 36 patients without enuresis

Inclusion/Exclusion Criteria

Inclusion: night time and or day time wetting.
Exclusion: anatomical neurological abnormalities,or mentally retarded children.

Patient Characteristics

Enuresis group: 75% were male, the mean age was 10 years, 77% had night time wetting, and 23% had night and day time wetting.
Control group: 51.4% were male, and the mean age was 10.2 years.

There was a statistically significant difference in distribution of gender types of the two groups.

Recruitment

Second visit to Paediatric Uro/Nephrologic Centre.

Setting

The Ghent University Hospital, Belgium.

Interventions/ Test/ Factor being investigated	The Social Anxiety Scale for Children (SAS-C), the state-trait anxiety inventory for children (STAI-C), The shortened depression questionnaire for children (SDQ-C), The Self-Perception Profile for Children by Harter (SPP-C),and Child Behaviour Checklist (CBCL).
Comparisons	Between children with enuresis and without enuresis.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Scores on the measurement scales.
Results	The Social Anxiety Scale for Children (SAS-C) – measures cognitive and affective anxious reactions in different situation in 9 to 12 years old children. The state-trait anxiety inventory for children (STAI-C) – self reported inventory measure instrument to identify situation anxiety in 8 to 15 years old children, contains 20 sentences which refer to the feelings of the child at a certain moment. The shortened depression questionnaire for children (SDQ-C) – 9-item scale is a shortened version of the depression questionnaire for children and was developed for early identification of depressive or declining depressive children. The Self-Perception Profile for Children by Harter (SPP-C) – measures self-concept in 8 to 12 year of children and consists of 6 subscales. Child Behaviour Checklist (CBCL) – 3 broadband scales of internalising, externalising and total problems, study only used withdrawal, somatic complaints, anxious/depressive and social problem, a T-score of 63 or higher was considered clinical. Results of CBCL score: Comparing children with enuresis and children without enuresis the following were statistically significantly different: the raw score for withdrawal and the raw score for anxious/depressive; the t scores for internalising problems and total problems. The following were not statistically significantly different: the raw score for physical complaints and social problems. The study showed for children within the clinical range of the CBCL score for internalizing problems in the enuresis group 19.7% compared to 11.6% in the control group; for internalizing problems in the enuresis group 20.4% compared to 6.1% in the control group. Results of the SAS-C, STAI-C, SDQ-C and SPP-C scores: Comparing children with enuresis and children without enuresis the following were statistically significantly different: on the SAS-C score was social desirability. The following were not statistically significantly different: on the SAS-C score – social situations, intellectual situations, athletic situations, physical appearance, cognitive reactions, emotional reactions, total anxiety; the STAI-C score, the SDS-C score, on the SPP-C score – scholastic competence, social acceptance, athletic competence, physical appearance, behavioural conduct, global self worth. The study compared correlations between CBCL and SPP-C, STAI-C and SDQ-C for the entire sample: there was a statistically significant difference for SPP-C score compared to CBCL score for social acceptance, behavioural conduct and global self worth. There was no statistically significant difference between the STAI-C and SDQ-C scores and CBCL scores. The study compared correlations between CBCL and SPP-C, STAI-C and SDQ-C for the children with enuresis: there was no statistically significant difference for SPP-C, the STAI-C and SDQ-C scores compared to CBCL score.
Safety and adverse effects	None reported.
Does the study answer the question?	There was a statistically significant difference between children with NE and children without NE on the CBCL score for the raw score for withdrawal and the raw score for anxious/depressive, and the t scores for internalising problems and total problems; and on the SAS-C score for social desirability.
Effect due to factor in study?	There was a statistically significant difference between children with NE and children without NE.
Consistency of results with other studies?	No other similar studies.

Directly applicable to guideline population?	Children had a mean age of 10 years in the NE group and 10.2 years in the control group.

Internal Validity

Yeung CK;Chiu HN;Sit FK;

Bladder dysfunction in children with refractory monosymptomatic primary nocturnal enuresis

Ref ID 650 1999

Study Type Cohort **Funding** Not reported.

Number of participant	N=46
Inclusion/Exclusion Criteria	Inclusion: monosymptomatic priamry nocturnal enuresis with treatment failure defined as non-response (failure to achieve an average decrease of 50% or greater in bedwetting frequency weekly during therapy) or significant relapse of enuretic symptoms to 3 or more wet nights weekly after stopping treatment. Exclusions: any identifiable urinary symptoms other than nocturnal enuresis.
Patient Characteristics	37 chinese boys and 9 girls. Aged 7 to 15 years old (mean age 10.2). The participants had monosymptomatic primary nocturnal enuresis (3 or more nights weekly) and had treatment failure. Previously the participants had been part of an interhospital prospective treatment study of primary nocturnal enuresis and had 12-weeks of oral desmopressin with or without an enuretic alarm.
Recruitment	Not reported.
Setting	Evaluation done in hostpital. Assume in China?
Interventions/ Test/ Factor being investigated	Bladder dysfunction through urodynamic study(day) and EEG and cystometry monitoring (night).
Comparisons	Not reported.
Length of Study/ Follow-up	None reported.
Outcome measures studied	Daytime and nighttime urinary output; functional bladder capacity; decrease of 50% or greater in no. of wet nights during treatment.
Results	Evaluations were done by natural and conventional filling urodynamic study in the daytime and simultaneous EEG and cystometry monitoring during sleep at night. The study wrote that: pattern 1 - normal daytime urodynamics with significant bladder instability at night with normal volume voiding precipitated by unstable detrusor contractions in 14 boys(34%). Pattern 2- normal daytime urodynamics with frequent small volume voiding at night, probably representing latent bladder instability, in 4 boys (10%). Pattern 3 involved abnormal daytime urodynamics with small bladder capacity, a discoordinated daytime voiding pattern and marked nighttime bladder instability associated with poor sleep in 6 boys (15%). Pattern 4 was abnormal daytime urodynamcis with an obstructive pattern, and marked daytime and nighttime detrusor hypercontractility (mean maximum detrusor pressure 178 cm water) in 8 boys (20%). Pattern 5 was abnormal daytime urodynamics with a dysfunctional daytime voiding pattern and frequent small volume nighttime voiding in 8 girls and 1 boy (22%). The home recordings of urinary output showed the majority of patients had a daytime to nightime urinary output ratio of greater than 1 (mean 2.43, range 0.89 to 6.32). Almost none had nocturnal polyuria (table 1). Table 1: daytime and nighttime urine output: Mean urine output +/- s.d (ml):

pattern	daytime	nighttime	mean daytime/nighttime output +/- s.d
1	810 +/- 291	360 +/-222	2.92 +/-1.77
2	1182 +/- 348	596 +/-364	2.31 +/-0.89
3	797 +/- 72	423 +/-224	2.44 +/-1.27
4	818 +/- 196	433 +/-67	1.98 +/-0.75
5	868 +/- 78	436 +/-129	2.15 +/-0.69
overall:	867 +/-244	429 +/-209	2.43 +/-1.24

Functional bladder capacity ranged from 60 to 380ml (mean 192) which was closely correlated with bladder capcity on cystometry during natural filling urodynamics (table 2).

Table 2: functional bladder capacity

	Mean Bladder capacity +/- s.d (ml)			
pattern	cystometric capacity	functional	expected for age	% functional/expected
1	252 +/-103	247 +/-95	343 +/-67	72 +/-23
2	233 +/-30	210 +/-26	353 +/-75	62 +/-19
3	129 +/-123	167 +/-88	355 +/-79	49 +/-27
4	92 +/-58	118 +/-51	390 +/-57	30 +/-9
5	174 +/-77	197 +/-71	385 +/-69	53 +/-22
overall	178 +/-106	192 +/-85	364 +/-67	54 +/-25

A 4-week course of 400micrograms desmopressin orally at bedtime still produced a significant response - greater than 50% decrease in the number of wet nights during treatment in 47% of the patients, although symptoms relapsed on stopping therapy in all.

Response to desmopressin therapy

	Mean no. wet nights/week +/- s.d		
Pattern	before therapy	during therapy	% patients signficantly improved
1	5.9 +/- 1.5	3.7 +/- 3.0	50
2	5.5 +/- 1.0	1.3 +/- 1.8	75
3	5.2 +/- 1.1	2.3 +/- 2.8	60
4	5.0 +/- 1.1	2.3 +/- 1.7	50
5	4.6 +/- 1.7	3.4 +/- 1.8	14
overall	5.3 +/- 1.4	2.9 +/- 2.4	47

Safety and adverse effects

None reported.

Does the study answer the question?

All patients had a small functional bladder capacity compared with that expected of their age and they voided small volumes frequently. This finding was associated with various patterns of bladder dysfunction.

They concluded that monosymptomatic nocturnal enuresis is a heterogeneous condition consisssting of a spectrum of disorders and various types of bladder dysfunction that probably contribute significantly to its pathogenesis, especially in patients with treatment failure and refractory symptioms. Nocturnal enuresis may be the only symptom even in children with gross underlying bladder dysfunction.

Effect due to factor in study?

Consistency of results with other studies?

No other similar studies

Directly applicable to guideline population?

Aged 7 to 15 years old, mean age 10.4 years and had primary monosymptomatic NE.

Internal Validity

Question: What is clinical and cost effectiveness of additional

investigation and treatment in children who have not responded to an adequate trial of both desmopressin and or alarms?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Aladjem M;Wohl R;Boichis H;Orda S;Lotan D;Freedman S;

Desmopressin in nocturnal enuresis

Ref ID 477 1982

Study Type	Randomised Controlled Trial	**Funding**	Study states desmopressin was Ferring AB, Sweden but does not report funding.

Number of participant	32 in total: 15 in group A and 17 in group B.
Inclusion/Exclusion Criteria	Inclusion: enuretic children. Exclusion: organic disease of the urinary tract
Patient Characteristics	The age range was 7-15 years. In group A 7 out of 15 were boys and the mean age was 10.5 years. The mean number of wet nights in the baseline 30 night period was 18.7 (SD 6.5), 12 had previously tried clorimipramine hydrochloride (2 of which had responded). 4 had a family history of NE. In group B 8 out of 17 were boys and the mean age was 10 years. The mean baseline number of wet nights in 30 night baseline period was 21.3 (SD 8.3). 11 had previously tried clorimipramine hydrochloride (3 of which had responded). 6 had a family history of NE. 3 patients had a history of UTI and of healed vesicoureteric reflux
Recruitment	Not reported
Setting	Israel
Interventions/ Test/ Factor being investigated	Group A: 10 micro grams intranasal desmopressin Group B: intranasal placebo
Comparisons	Between groups A and B.
Length of Study/ Follow-up	90 days.
Outcome measures studied	Number totally dry, number of wet nights during final month and at follow up.
Results	Treatment for 30 days Number of children who achieved total dryness: In group A (desmopessin) 6 out of 15 chidlren achieved total dryness compared to 1 out of group B (placebo). Mean number of wet nights in final month: In group A (desmopressin) the mean number of wet nights during final month was 6.5 (SD 9.2) and in group B (placebo) was 18.8 (SD 8.3). Mean number of wet nights at follow up: In group A (desmopressin) the mean number of wet nights was 15.7 (SD 8.9) and in group B (placebo) was 16.9 (SD 9.4). The study reported a significant difference in response dependant on age. Only children aged over 10 years became completely dry and the only failures were ages under 10 years (3 failures in total). Response rate to desmopressin: As early as 1-3 days

Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that more children became dry with desmopressin and children on desmopressin had fewer wet nights at the end of treatment but there was little difference in the number of wet nights at end of treatment and the number of wet nights at follow up.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	
Directly applicable to guideline population?	Age range 7-15 years.
Internal Validity	Unclear allocation concealment

Austin PF;Ferguson G;Yan Y;Campigotto MJ;Royer ME;Coplen DE;

Combination therapy with desmopressin and an anticholinergic medication for nonresponders to desmopressin for monosymptomatic nocturnal enuresis: a randomized, double-blind, placebo-controlled trial

Ref ID 3902 2008

Study Type Randomised Controlled Trial **Funding** National Kidney Foundation

Number of participant	34 patients, 16 in desmopressin and placebo, 18 in desmopressin and tolterodine
Inclusion/Exclusion Criteria	Inclusion: aged 6 to 17 years, monosymptomatic primary NE, failed treatment of tablet 0.6mg desmopressin as monotherapy (both partial and non response), 4 wet nights a week Exclusion: PUT symptoms, bowel elimination problems (eg encopresis or consitpation), day time wetting, increased or descrease voiding frequency, receiving anticholinergic treatment, know allery to anticholingergics used for bladder relaxation, any history of gastric retention, uncontrolled narrow-angle glaucoma.
Patient Characteristics	In the desmopressin and placebo group the mean age was 10.5 (sd 2.25) years, 12 out of 16 were male, the mean number of wet nights was 6.56 (sd 0.81) per week at baseline. In the desmopressin and tolterodine group the mean age was 10.56 (sd 2.28) years, 12 out of 18 were male, the mean number of wet nights was 6.22 (sd 1.16) per week at baseline
Recruitment	Patients referred to paediatric clinic for treatment of NE
Setting	Paediatric clinic, USA
Interventions/ Test/ Factor being investigated	Group A: 0.6 mg Desmopressin and placebo Group B: 0.6 mg desmopressin and 4 mg tolterodine
Comparisons	Between groups A and B
Length of Study/ Follow-up	1 months
Outcome measures studied	Number of children who achieved 14 consecutive dry nights, Number of children who achieved >50% improvements in the number of dry nights
Results	1 month of treatment Number of children who achieved 14 consecutive dry nights: In group A (desmopressin and placebo) 1 out of 16 achieved 14 consecutive dry nights compared to 3 out of 18 in group B (desmopressin and tolterodine).

	Number of children who achieved >50% improvements in the number of dry nights: In group A (desmopressin and placebo) 4 out of 16 achieved >50% improvements in the number of dry nights compared to 5 out of 18 in group B (desmopressin and tolterodine)
Safety and adverse effects	None reported
Does the study answer the question?	The study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights and the number of children who achieved greater than 50% improvement in the number of dry nights between children treated with desmopressin and placebo and children treated with desmopressin and tolterodine
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other studies consider this comparison in this population
Directly applicable to guideline population?	Children had a mean age od 10.5 and 10.56 years
Internal Validity	Unclear allcoation concealment

Neveus T;Tullus K;

Tolterodine and imipramine in refractory enuresis; a placebo-controlled crossover study

Ref ID 18 2008

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	27 in total (25 after 2 drop outs).
Inclusion/Exclusion Criteria	Inclusion: primary NE, wet at least 7 nights in 2 weeks, unresponsive to both desmopressin and alarms when treated for 6 months. Exclusion: concomitant cardiac, nephrologic, metabolic or neurologic disease, UTI, previous treatment with anitcolinergic or tricyclic drug, or day time wetting.
Patient Characteristics	The mean age was 9.4 (SD 2.1) years, age range 6-13 years. 22 out of 27 were boys. 7 children had monosymptomstic NE, 17 had urgency, 16 had previously been daytime incontinent, 3 had increased daytime microturition frequency, and 8 suffered from constipation. The mean baseline wetting was 11 (SD 3.6) in 2 weeks.
Recruitment	Not reported.
Setting	Sweden.
Interventions/ Test/ Factor being investigated	Group A: 1-2mg tolterodine at bedtime (higher dose given to children aged over 8 years) Group B: 25-50 mg imipramine at bedtime (higher dose given to children aged over 8 years) Group C: placebo
Comparisons	Between treatment groups.
Length of Study/ Follow-up	None.
Outcome measures studied	Full and partial response, mean number of wet nights in last 2 weeks of trial, adverse events, and numbers who dropped out.
Results	5 weeks of each treatment. Children underwent a 2 week observation period and then 2 weeks of 0.4 mg desmopressin at bedtime to ensure only therapy resistant children were included.

Full response
5 out of 25 responded to imipramine, 0 out of 25 responded to tolterodine or placebo.

>50% improvement
2 out of 25 had a partial response to imipramine only and 1 out of 25 children had a partial response to tolterodine. 0 out of 25 had a partial response to placebo.

Mean number of wet nights in last 2 weeks of treatment:
In the tolterodine group the mean number of wet nights in the last 2 weeks of treatment was 10.4 (SD 3.9), in the imipramine group the mean was 7.8 (SD 5.1) and in the placebo group the mean was 11 (SD 3.9).
Imipramine was significantly better than the placebo (p=0.001) and significantly better than tolterodine (p=0.006).

Number of drop outs:
In the imipramine group 1 child dropped out due to nausea and in the placebo group 1 child dropped out due to becoming spontaneously dry.

Adverse events:
In the group treated with imipramine, 3 children had slight mood changes, 2 had insomnia, 1 had palpitations, and 2 had slight nausea (1 of which dropped out). In the group treated with tolterodine 1 child had slight mood change. There were no adverse events in the placebo group.

Safety and adverse effects

Imipramine: 3 children had slight mood changes, 2 had insomnia, 1 had palpitations, and 2 had slight nausea (1 of which dropped out).
Toloterodine: 1 had slight mood change.
Placebo: none

Does the study answer the question?

The study showed that imipramine was more effective in giving a full response, it also showed that imipramine was significantly better than both tolterodine and placebo treatment.

Effect due to factor in study?

Yes

Consistency of results with other studies?

No other studies to compare to.

Directly applicable to guideline population?

Age range 6-13 years.

Internal Validity

Unclear allocation concealment

Stenberg A;Lackgren G;

Desmopressin tablets in the treatment of severe nocturnal enuresis in adolescents

Ref ID 1711 1994

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant

10 patients were allocated either to placebo or desmopressin tablets.

Inclusion/Exclusion Criteria

Inclusion criteria: adolescents (12 years or older) suffering from severe Primary NE, defined as a mininum of 3 wet nights per week during an observation period of 2 weeks. Exclusion criteria: daytime wetting, urinary tract infection, or urinary tract abnormalities. Patients could have not been treated with any conditioning device or any other antienuretic regimen 2 weeks before entry into the study.

Patient Characteristics

20 males and 5 females with a mean age of 13.5 years (range 11 to 21 years) median 13.0. Baseline wetting 4.7 (SD 1.1) wet nights per week. All patients but three had previously used the bell and pad conditioing system with no improvement. 15 patients had been treated with antidepressant drugs. Other drugs, which had failed were: ephedrine (4 patients) and terodiiline, propantheline, and emepromium bromide (1 patient each). 9 patients had a family history of enuresis.

Recruitment	Not reported.
Setting	Children's hospital. Sweden
Interventions/ Test/ Factor being investigated	First 2 week single blind titration period was started and 200 and 400micrograms of desmopressin were administered. All patients were given diary cards and the registration of dry and wet nights was done by the parents. For the long-term treatment period, each patient was given the lowest dosage of demopressin that reduced the number of wet nights by 50% or more. The patients who did not have a reduction in wet nights continued on the 400microgram dose. Double-blind period During the first 2 weeks the first 10 patients were allocated to placebo or desmopressin tablets. After 2 weeks treatment, each patient was crossed over to the alternate therapy. This was a separate part of the study and all patients who were included in the double blind part continued with the long-term studies. Long term treatment period- open period with two 12 week spans with demopressin treatment each followed by a 2 week observation period without use of medication. Patients were then divided into 1) full responders, with just 1 wet night; 2)intermediate responders with two to 3 wet nights, and 3)nonresponders with more than 3 wet nights per week. No significant crossover period occurred between full responders and nonresponders.
Comparisons	Desmopressin versus placebo
Length of Study/ Follow-up	Follow up for 2 weeks after treatment.
Outcome measures studied	Mean number of wet nights, adverse events
Results	First 2 week single blind titration period- during this period the mean number of wet nights per week was 4.9 ± 1.2 and during the dose titration for the first week when the patients received 200 micrograms, the mean number of wet nights was 2.8 ± 2.2. In the second week of dose titration the patients received a daily dose of 400micrograms. The mean number of wet nights 2.4 ± 2.3. Througout the dose titration period, there was a decrease of about 50% in bed wetting compared to the observation period. Double-blind period- The mean basline value of wet nights per week was 4.7 ± 1.1. During the 2 weeks on desmopressin, the mean number of wet nights was reduced to 1.8 ± 1.4. The corresponding value for the placebo period was 4.1 ± 1.5. the difference between placebo and desmopressin in mean number of wet nights was 2.35 units wth a 95% confidence interval for the population difference from 1.5 to 3.1 Long term treatment period I- -23 patients entered the first long term treatment period. The number of wet nights for the whole group was 2.0 ± 2.1. Eleven patients were full responders, 5 intermediate and 7 did not respond to the drug. Midtreatment observation period- mean number of wet nights per week increased to 3.0 ± 2.3. 1 patient did not turn up for follow up. Long term treatment period II- 17 patients entered the second long term period, 3 on 200micrograms tablets and 14 on 400 micrograms daily. The mean number of wet nights per week for the whole group was 1.7 ± 1.7. the mean number of wet nights for the intermediate responders was 2.3 ± 1.2. 6 patients never started this treatment Posttreatment observation period- 16 patients were followed up for 2 weeks and the number of wet nights per week was 2.8 ± 2.4. Side effects: 5 children suffered from headache, 6 from abdominal pain and 1 from nausea and vertigo

Safety and adverse effects	the total weight gain was 5%. 1 patient had an increase in blood pressure during the first part of the second long-term period and was excluded from the last 6 weeks of this period. Most common complaints were headache and abdominal pain, which occurred in 5 and 6 patients, respectively. The symptoms disappeared during treatment. 1 patiens also complained of nausea and vertigo.
Does the study answer the question?	
Effect due to factor in study?	There is a risk of bias: randomisation not clearly described and ITT not reported. Age range of participants is from 11 to 21 years, with mean age of 13.5 years.
Consistency of results with other studies?	
Directly applicable to guideline population?	Relevant comparisons.
Internal Validity	Unclear allocation concealment

Terho P;Kekomaki M;

Management of nocturnal enuresis with a vasopressin analogue

Ref ID 460 1984

Study Type	Randomised Controlled Trial	**Funding**	Not reported

Number of participant	49 children
Inclusion/Exclusion Criteria	Inclusion criteria: aged 7-17 years with serious nocturnal wetting. Exclusion: day time wetting or faecal soiling; voiding difficulties; obvious neurological abnormalities; and diurnal wetting.
Patient Characteristics	80% had failed treatment with imipramine and were aged 7 to 16 years. 49 had awakening protocol: 46 had water deprivation; 43 had tricyclic antidepressants 13 had psychological counseling; 2 had alarm device and 1 had no previous treatment.
Recruitment	Not reported.
Setting	Finland
Interventions/ Test/ Factor being investigated	Group A: 20 micro grams desmopressin Group B: placebo
Comparisons	Between desmopressin and placebo.
Length of Study/ Follow-up	4 weeks of follow up
Outcome measures studied	Mean number of wet nights
Results	3 weeks of treatment Mean number of wet nights Group A (desmopressin) had a mean number of wet nights of 30.9 (sd 28.7) while Group B (placebo) had a mean number of wet nights of 57.5 (sd 26.1).
Safety and adverse effects	None reported

Does the study answer the question?	The study shows children treated with desmopressin had fewer wet nights compared to children treated with placebo.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Not clear.
Directly applicable to guideline population?	Children had an age range of 7 to 16 years.
Internal Validity	No wash out

Tuvemo T;

DDAVP in childhood nocturnal enuresis

Ref ID 495 1978

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	18 children in total. 8 patients received intervention in the first 28 day period and 10 received it in the second 28 day period.
Inclusion/Exclusion Criteria	#Deleted
Patient Characteristics	Age: ranged 6-12 years. Previous treatment: children had not responded satisfactorily to previous treatment with imipramine or amitriptyline. Baseline wetting: mean (SEM) number of dry nights out of 28: 7.5 (2.98).
Recruitment	Not reported.
Setting	University Hospital, Sweden.
Interventions/ Test/ Factor being investigated	A: Intervention group received 20 micro-grams intranasal DDAVP (minerin) just before bedtime after emptying bladder. B: Identical placebo as above (crossover trial). 28 days in each condition.
Comparisons	Placebo then intervention (crossover trial).
Length of Study/ Follow-up	No follow-up
Outcome measures studied	Mean number of dry nights out of 28. Side effects. Number of children whose results were said to be excellent. Follow-up after 6 months.
Results	#Deleted
Safety and adverse effects	Not reported.
Does the study answer the question?	#Deleted
Effect due to factor in study?	Not sure. No power calculation given and only 18 participants with no clear allocation concealment.
Consistency of results with other studies?	

Directly applicable to guideline population?	Intervention and population was of interest to the guideline, few of the outcomes reported were those relevant to the guideline.
Internal Validity	Unclear allocation concealment

Tuygun C;Eroglu M;Bakirtas H;Gucuk A;Zengin K;Imamoglu A;

Is second-line enuretic alarm therapy after unsuccessful pharmacotherapy superior to first-line therapy in the treatment of monosymptomatic nocturnal enuresis?

Ref ID 32 2007

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	84 patients in total, 35 in group A, 49 in group B and 19 in group C
Inclusion/Exclusion Criteria	Inclusion: monosymptomatic nocturnal enuresis, wet at least 3 times a week during the last 3 months Exclusion: Diurnal enuresis, polyuric disorders, genitourinary system abnormalities, neurological disorders, recurrent UTIs
Patient Characteristics	The median age was 8 years (range 6-13 years). The ratio of male/ female was 3/2. There was no significant difference between the three group's age or sex. 71.73% had at least one parent with a history of enuresis. At baseline 54.34% were wet 25-30 nights a month, 20.65% were wet 20-25 nights a month and 25% were wet 15-20 nights a month.
Recruitment	Not reported
Setting	Turkey, treatment at home
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: desmopressin Group C: those who were in group B but did not become dry were changed to have alarm treatment
Comparisons	Between groups A, B and C
Length of Study/ Follow-up	6 months
Outcome measures studied	>90% decrease in number of wet nights, 50-90% decrease in number of wet nights, relpase at 6 months, change in number of wet nights
Results	Treatment was for 3 months >90% decrease in number of wet nights: After 3 months of treatment in group A (alarm) 20 out of 35 children (57.14%) had achieved a >90% in number of wet nights compared to 25 out of 49 (51.02%) in group B (desmopressin) and 13 out of 19 (68.42%) in group C (desmopressin then alarm). These differences were not significant. 50-90% decrease in number of wet nights: After 3 months of treatment in group A (alarm) 9 out of 35 children (27.71%) had achieved a 50-90% in number of wet nights compared to 15 out of 49 (30.61%) in group B (desmopressin) and 3 out of 19 (15.78%) in group C (desmopressin then alarm). These differences were not significant. Relapse at 6 months: At 6 months 10 out of 35 children (28.57%) had relapsed compared to 27 out of 49 (55.10%) in group B (desmopressin) and 6 out of 9 (31.57) in group C (desmopressin then alarm). The difference between groups A and B was significant p=0.008 but the difference between groups A and C was not significant. Change in mean number of wet nights: In group A (alarm) at baseline the mean number of wet nights per month was 23.2 (SD 6.23) at the end of treatment it was 3.41 (SD7.68), this difference was significant p<0.001. In group B (desmopressin) at baseline the mean number of wet nights per

	month was 23.44 (SD 6.3) at the end of treatment it was 10.7 (SD 10.94), this difference was significant p<0.001. In group C (desmopressin then alarm) at baseline the mean number of wet nights was 28 (SD 1.37) at the end of treatment it was 5.5 (SD 10.65), this difference was significant p<0.001. The difference between groups A, B and C was also significant p=0.008.
Safety and adverse effects	none reported
Does the study answer the question?	The study showed that treating children with an alarm was more effective than desmopressin in reducing the number of wet nights, it also showed that if patients did not respond to desmopressin treating them with an alarm did lead to a reduction in the number of wet nights. The study showed that few children who were treated with an alarm, both as initial treatment and as secondary treatment were significantly less likely to relapses than those treated with desmopressin. All groups had a significant reduction in the mean number of wet nights per month.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	Children were aged between 6-13 years
Internal Validity	

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Butler RJ;Brewin CR;Forsythe WI;

A comparison of two approaches to the treatment of nocturnal enuresis and the prediction of effectiveness using pre-treatment variables

Ref ID 27 1988 l

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	74 in total
Inclusion/Exclusion Criteria	Inclusion: Aged over 6 years, wetting at least 5 times a week for a month, normal clinical examination, normal urine on microscopy, normal intelligence, not having any form of enuresis-related drug or psychotherapeutic treatment
Patient Characteristics	76% were boys, The mean age was 9.7 years (range 6.1-14.4 years). 48.6% has previously been treated with an alarm. In the DBT group 66% had previously been treated with an alarm compared to 25% in the alarm group.
Recruitment	Patients were referred as out patients for treatment of NE.
Setting	Leeds, UK. Treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: MDBT with alarm but without reprimands
Comparisons	Between groups A and B
Length of Study/ Follow-up	16 weeks.
Outcome measures studied	Numbers of children dry for 14 consecutive nights, change in number of wet nights, and number of dropouts.
Results	Modified dry bed training removed the punitive elements. 16 weeks treatment The drop out rates were 8 in the alarm group and 2 in the DBT-M group. Four more were terminated by agreement early in the DBT-M group. 14 consecutive dry nights were achived by 20 out of 28 children in the alarm group and 15 out of 35 in the DBT group. The baseline number of dry nights (during 4 week baseline period) was 1.02 for the DBT-M group and 1.07 for the Enuresis Alarm, $t<1$, $p>0.10$. The number of dry nights in the last 4 weeks of treatment was 23.79 for the DBT-M group and 20.76 for the enuresis alarm group. The differences between all outcome measures were not statistically significant. The mean number of wet nights per week at end of treatment for the alarm was 1.81 compared to 1.05 for the dry bed training.
Safety and adverse effects	None reported.
Does the study answer the question?	A modified version of the Dry Bed Training was compared to the standard enuresis alarm treatment. The DBT-M was an alarm plus training in comparision to just an alarm. Both had success rates of 70%. The author concludes that the additional procedures involved in DBT-M do not seem to increase effectiveness substantially maybe due to the amount of training given (one night).

Effect due to factor in study?	Yes.
Consistency of results with other studies?	
Directly applicable to guideline population?	Children were aged over 6 years.
Internal Validity	Unclear allocation concealment and blinding

Butler RJ;Forsythe WI;Robertson J;

The body-worn alarm in the treatment of childhood enuresis

Ref ID 362 1990

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	In study 1: 40 in total, 20 in each group In study 2: 48 in total, 24 in each group (Study 2 included children previously resistant to treatment)
Inclusion/Exclusion Criteria	Inclusion: wet at least 4 nights a week for a month, normal physical examination, normal urine microscopy, normal intelligence, not previously treated for NE with any conditioning method (except alarms), previously unsucessful with pad and bell alarm, and no associated diurnal enuresis.
Patient Characteristics	The mean age was 10.6 years (range 7.4-14.7 years). 81% were boys. In group A the mean age was 10.2 years, the baseline number of dry nights was 1.2, and the male to female ratio was 19:5. In group B the mean age was 11.1 years, the baseline number of dry nights was 1.3, and the male to female ratio was 20:4. All patients had previously been unsucessfully treated with pad and bell alarm.
Recruitment	Referred as out-patients for treatment of NE (in both studies).
Setting	Leeds, UK, treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: MDBT with alarm (pad and bell) Group B: alarm (body worn)
Comparisons	Between group A and B.
Length of Study/ Follow-up	6 months
Outcome measures studied	Dry for 14 consecutive nights, number of wet nights, relapses
Results	Modified dry bed training removed the punitive elements. 16 weeks treatment 14 consecutive dry nights: In group A (DBT) 14 out of 24 children achieved 14 consecutive dry nights compared to 20 out of 24 in group B (alarm). The difference was not statistically significant. The mean number of wet nights before achieving 14 consecutive dry nights was 53.7 in group A (DBT) and 40.7 in group B (alarm). There was an immediate response with both interventions, and from week 3 the body-worn alarm group consistently achieved more dry nights. The difference was significant at week 3 ($t=2.28$, $df=43$, $p<0.05$); and week 4 ($t=2.26$, $df=42$, $p<0.05$). At week 7 the children in the MDBT group achieved the same number of dry nights as the body-worn alarm group did in week 3. Mean number of wet nights in 16 weeks

	In group A (DBT) the mean number of wet nights was 28.7 compared to 25 in group B (alarm). The difference was not statistically significant. The mean number of wet nights per week at end of treatment for the alarm was 1.6 compared to 1.8 for the MDBT. Number of children who relapsed: 7 out of 14 of the DBT group relapsed within 6 months, and 9 out of 20 relapsed in the alarm group. Number of drop outs: 1 out of 24 children dropped out of the alarm group compared to 2 out of 24 in the DBT group.
Safety and adverse effects	None reported
Does the study answer the question?	It compares two types of alarms, the body-worn alarm and the pad and bell (modified dry-bed training). Both were equally effective in the first study (70%) and the second study initial arrest was 58% for the MDBT group and 83% for the body-worn alarm group, however the difference was not significant. The body-worn alarm achieved a greater number of dry nights earlier than the other group. The relapse rate was higher in the second study than the first study, the difference between groups was not significant.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	
Directly applicable to guideline population?	Children were aged between 6.1 years and 15.6 years
Internal Validity	Unclear allocation concealment and blinding

Dimson SB;

DDAVP and urine osmolality in refractory enuresis

Ref ID 436 1986

Study Type Randomised Controlled Trial **Funding** Ferring Pharmaceuticals

Number of participant	17 in total in this cross over trial.
Inclusion/Exclusion Criteria	Inclusion: failed to responded to drugs or alarm, and aged 6-13 years. Exclusion: organic cause of NE, UTI, more dry nights than wet in baseline period of 2 years, or had been dry between 2 and 3 1/2 - 4years.
Patient Characteristics	14 were boys, the age range was 6-13 years, baseline wetting was greater than 50% wet nights during a 2 week observation period. 3 children had encopresis. All children had failed to respond to alarms and drug treatment (study reposts drug treatment to be mainly imipramine and amitriptyline).
Recruitment	Patients who attended enuretic clinic Woolwich, east London, UK.
Setting	London, UK.
Interventions/ Test/ Factor being investigated	Group A: intranasal desmopressin (20 micro grams) Group B: matching placebo
Comparisons	Between groups A and B.
Length of Study/ Follow-up	2 weeks.

Outcome measures studied	Numbers of children achieving 14 consecutive dry nights, mean number of wet nights after 2 weeks of treatment, and numbers relapsing.
Results	2 weeks of treatment Number of children who achieved 14 consecutive dry nights: In group A (desmopressin) 2 out of 17 children achieved 14 consecutive dry nights compared to 0 in group B (placebo). Relapse All children relapsed after trial ended (17 out of 17). Mean number of wet nights per week: In group A (desmopressin) the mean number of wet nights was 3.4 compared to 5.0 in group B (placebo). There were no side effects.
Safety and adverse effects	None
Does the study answer the question?	The study showed that children were more likely to become dry when treated with desmopressin and have fewer wet ngihts than when treated with placebo.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Aged 6-13 years.
Internal Validity	Unclear allocation concealment and blinding

Fjellestad-Paulsen A;Wille S;Harris AS;

Comparison of intranasal and oral desmopressin for nocturnal enuresis

Ref ID 429 1987

Study Type Randomised Controlled Trial **Funding** Ferring AB Malmo Sweden.

Number of participant	30 in total
Inclusion/Exclusion Criteria	Inclusion:primary nocturnal enuresis. Exclusion: organic causes of NE, day time wetting, UTI, diurnal wetting, faecal soiling, neurological or urological abnormalities, or more than 3 wet nights a week during baseline.
Patient Characteristics	There were 20 boys, the mean age was 9.8 (SD 2.5) years (range 6-15 years), and the mean number of dry nights at baseline was 2.2 (SD 0.2). 60% had failed to respond to alarms, 23% to desmopressin, 26% to tricyclics and 20% to anticholinergics.
Recruitment	Not reported.
Setting	Sweden.
Interventions/ Test/ Factor being investigated	Group A: oral desmorpessin 200 micro grams Group B: intransal desmopressin 20 micro grams Group C: placebo
Comparisons	Between treatment groups.
Length of Study/ Follow-up	6 weeks (2 weeks of each treatment)

Outcome measures studied	Mean number of dry nights, and numbers becoming totally dry.
Results	Patients had 2 weeks of placebo then 2 weeks of each treatment During treatments the mean number of dry nights was 4 in group A (oral desmopressin), 4.1 in group B (intranasal desmopressin) and 2.5 in group C (placebo). In group A (oral desmopressin) 2 patients became totally dry, compared to 1 in group B (intranasal desmopressin). At follow up 9 children were totally dry. Side effects: 2 patients had nasal discomfort and 3 complained of epistaxis (there was no difference between placebo and treatment arms).
Safety and adverse effects	2 patients had nasal discomfort and 3 complained of epistaxis (there was no difference between placebo and treatment arms).
Does the study answer the question?	The study showed that desmopresisn is more effective than placebo.
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	Age 6-15 years.
Internal Validity	Unclear allocation concelament and who was blinded

Gibb S;Nolan T;South M;Noad L;Bates G;Vidmar S;

Evidence against a synergistic effect of desmopressin with conditioning in the treatment of nocturnal enuresis

Ref ID 233 2004

Study Type	Randomised Controlled Trial	**Funding**	Research grant from Ferring Pharmaceuticals to the Mudoch Children's Reseach Institute.

Number of participant	207 patients: 101 in group A and 106 in group B.
Inclusion/Exclusion Criteria	Inclusion: non-responders to desmopressin intranasal spray after 4 weeks of treatment, aged 6-16 years old and who wet the bed at least 2 a week. Exclusion: neuropathic bladder, urinary tract abnormality, cystic fibrosis, allergic rhinitis, UTI in the previous 2 weeks, or taking imipramine or diuretics.
Patient Characteristics	In group A (desmopressin and alarm) 63% were male, the mean age was 8.5 (1.78 SD), the mean number of wet nights in the preceeding 28 nights was 23.9 (5.05 SD), 45% had a positive family history, 14% had secondary enursis, and 11% had day time wetting. 37% had previously tried alarms and 31% had previously tried medication for treatment of NE. In group B (placebo and alarm) 73% were male, the mean age was 8.3 (1.93 SD), the mean number of wet nights in the preceeding 28 nights was 23.7 (5.83 SD). 42% had a positive family history, 8.5% had secondary enursis, 7.5% had day time wetting. 31% had previously tried alarms and 26% had previously tried medication for treatment of NE.
Recruitment	Children were recruited from the general paediatric out-patient clinic at the Royal Children's hospital Melborne.

Setting	At home.
Interventions/ Test/ Factor being investigated	Group A: 20 - 40 micro grams desmopressin (nasal spray) and alarm (pad and bell) Group B: placebo (nasal spray) and alarm (pad and bell)
Comparisons	Between group A and B
Length of Study/ Follow-up	2 months
Outcome measures studied	Number of children achieving 28 dry nights, wet nights during treatment, drop outs, and adverse events.
Results	The study ran a 4-week "run in" of 358 patients treated with intranasal desmopressin. After 4 weeks non responders were randomised to two groups: group A had desmopressin internasal spray and alarm (pad and bell) and group B had a placebo nasal spray and alarm (pad and bell). Number achieving 28 dry nights: In group A (alarm and placebo) 51 out of 106 children achieved 28 dry nights compared to 52 out of 101 children in group B (alarm and desmopressin). Drop out: In group A (alarm and placebo) 17 out of 106 children dropped out compared to 9 out of 101 children in group B (alarm and desmopressin). Mean number of wet nights: In group A (alarm and placebo) the mean number of wet nights per week was 2.4 (sd1.53) compared to 1.8 (sd 1.13) in group B (alarm and desmopressin). Adverse events: 1 child who received desmopressin with alarm reported headaches. 1 child who received placebo with alarm reported nose bleeds. The authors noted that day wetters were more likely to be non-responders to desmopressin 71% (20 out of 28).
Safety and adverse effects	In group A 1 child suffered from headaches and in group B 1 child had nose bleeds.
Does the study answer the question?	The study showed a non-signficant difference in the number of patients achieving 28 dry nights between patients who received alarm with desmopressin and patients who received alarm with placebo. There was also a non-significant difference between the groups for the number of patients who relapsed and the change in number of wet nights.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Yes - age range was 6-16 years.
Internal Validity	Unclear allocation concealment and blinding

Terho P;

Desmopressin in nocturnal enuresis

Ref ID 390 1991

Study Type Randomised Controlled Trial **Funding** Does not say how funded. The author is from the Department of Health, Central School Clinic, Turku,

	Finland. Desmopressin was provided by Mr Per Wilhelmson, Ferring pharmaceuticals.
Number of participant	52 children in a crossover trial.
Inclusion/Exclusion Criteria	Inclusion: lifelong nocturnal enuresis; no diurnal wetting; no soiling; no urological or renal pathological conditions.
Patient Characteristics	Previous treatment: 52 had night awakening; 52 had fluid restriction; 29 had used tricyclic antidepressants; and 25 had used eneuresis alarms. Age range: 5-13 years; 35 boys and 17 girls. Baseline wetting: mean (SD) number of dry nights per week: 0.6 (0.2). Almost all patients had a family history of wetting.
Recruitment	Finnish School children. Does not say how recruited.
Setting	Turku, Finland.
Interventions/ Test/ Factor being investigated	A: intranasal desmopressin (20 micrograms) at bedtime rising to 40 micrograms if no response. B: placebo. Duration of treatment: 2 periods of 3 weeks in each condition. This part of the study was followed by a 3-week observation period.
Comparisons	Between treatment and placebo. Crossover trial.
Length of Study/ Follow-up	12 weeks treatment and 3 weeks observation period after the study.
Outcome measures studied	Mean number of dry nights per week; amount becoming totally dry during and after treatment; relapse after treatment; and side effects.
Results	Mean (SD) number of dry nights per week: The mean number of wet nights per week in the desmopressin group was 2.6 compared to 4.9 in the placebo group. All comparisons among the treatment options differed significantly ($p<0.01$). 15 (29%) children became totally dry during desmopressin treatment. 5 children remained dry after treatment. 47 patients relapsed after treatment. Side effects: non reported.
Safety and adverse effects	None reported.
Does the study answer the question?	The authors conclude that 'in a selected and severely enuretic population an increase from a mean of 0.6 to a mean of 4.5 dry nights per week with a dose of 20 micrograms desmopressin is regarded as a good response, although a further increase of dry nights would be welcomed.'
Effect due to factor in study?	Can not be sure. Description of the methodology is lacking.
Consistency of results with other studies?	
Directly applicable to guideline population?	The intervention and population are the interest of this guideline.
Internal Validity	Unclear allocation concealment

Vogt M;Lehnert T;Till H;Rolle U;

Evaluation of different modes of combined therapy in children with monosymptomatic nocturnal enuresis

Ref ID 4119 2009 Sep 17

Study Type Randomised Controlled Trial **Funding** Not stated.

Number of participant	N=43 children (Group A N=24, Group B N=19)
Inclusion/Exclusion Criteria	Inclusion criteria: patients aged >5 and <=15 years with monosymptomatic nocturnal enuresis. Exclusion criteria: treatment of enuresis within the last 12 months, daytime symptoms, or renal disease.
Patient Characteristics	13/43 children achieved dryness after initial monotherapy or discontinued treatment. Group A (N=16): female/male: 5/11, mean age: 6.7 (5-13), number of wet nights: 9.81 (sd 2.93) Group B (N=14): female/male: 7/7, mean age: 6.4 (5-13), number of wet nights: 10.5 (sd 3.59)
Recruitment	Patients attending the outpatient clinic were invited to take part in the study.
Setting	Outpatient clinic
Interventions/ Test/ Factor being investigated	Desmopressin followed by alarm treatment is compared to alarm treatment followed by desmopressin. Desmopressin was administered orally with an initial dose of 0.2mg (one tablet) for the first two weeks, followed by 0.4mg (two tablets) at night time for another 10 weeks.
Comparisons	Comparisons are made between Group A (initially treated with desmopressin) Group B (initially treated with alarm).
Length of Study/ Follow-up	Treatment for 12 weeks (desmopressin or alarm). For symptomatic only children, 12 weeks further treatment of desmopressin/alarm for Group A and alarm/ desmopressin for Group B. Final evaluation after 1 year.
Outcome measures studied	Complete dryness (maximum of 2 wet nights/ month, equals a 90% reduction of wet nights =response) in accordance to the standardization of the International Chiildren's Continence Society.
Results	After 12 weeks of treatment, 4/24 in Group A and 5/19 in Group B become dry and excluded from the treatment study. Another 4 children discontinued the treatment. The remaining 30 were included in the analysis (16 in Group A and 14 in Group B). After the 3 months of single therapy and 3 months of combined therapy, 11/16 children in Group A and 11/14 in Group B were dry (P>0.2). In total, 22/30 (73%) of children were dry, which consisted of 12/18 boys and 10/12 girls (P>0.2). Of the children with a normal maximum voided volume, 79% (19/24) achieved dryness, whereas only 3/6 children with small voided volumes become dry (P=0.3). 13/19 of children with nocturnal polyuria and 9/11 with no nocturnal polyuria became dry after 6 months (P=0.672).
Safety and adverse effects	Not described.
Does the study answer the question?	Yes. This study showed that combined therapy (desmopressin/alarm) can help children with MNE to achieve dryness in 73%. No significant difference was found between Group A and Group B, that is, the order of treatment.
Effect due to factor in study?	There was an unclear risk of selection and performance bias. No prior consideration of sample study was conducted. Uncertain that the overall effect is due to study intervention.
Consistency of results with other studies?	

Directly applicable to guideline population?	Direct.

Internal Validity

Grading: 2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

Kosar A;Arikan N;Dincel C;

Effectiveness of oxybutynin hydrochloride in the treatment of enuresis nocturna--a clinical and urodynamic study

Ref ID 663 1999

Study Type Cohort **Funding** Not reported

Number of participant	36 children
Inclusion/Exclusion Criteria	Inclusion: failure to respond to 25 mg imipramine for children aged 6 to 8 years and 50 mg imipramine from children aged over 8 years, wet at least 4 nights a week, stopped taking medication 2 months before the trial, no history of any other urological problem, and appeared healthy.
Patient Characteristics	Children had an age range of 6 to 18 years,and the mean baseline number of wet nights per week was 6.1 (sd 1.4). 3 children had spina bifida, 33.3% had a family history of bedwetting and 19.4% were wet in day time.
Recruitment	Attending clinic.
Setting	Turkey.
Interventions/ Test/ Factor being investigated	Oxybutinin.
Comparisons	No comparison.
Length of Study/ Follow-up	None reported.
Outcome measures studied	Mean number of wet nights per week.
Results	The study showed that in children treated with 15 mg daily oxybutynin the mean number of wet nights per week was 2.7 (sd 1.3) compared to a baseline wetting of 6.1 (sd 1.4) wet nights per week. The study did not present results for 10 mg daily oxybutynin or 20 mg daily oxybutynin.
Safety and adverse effects	None reported
Does the study answer the question?	The study showed oxybutinin reduced the mean number of wet nights per week in children who had failed to respond to imipramine.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other studies.
Directly applicable to guideline population?	Children were aged 6 to 18 years.
Internal Validity	Adequately addressed

Radvanska E;Kovacs L;Rittig S;

The Role of Bladder Capacity in Antidiuretic and Anticholinergic Treatment for Nocturnal Enuresis

Ref ID 785 2006

Study Type	Cohort	**Funding**	Slovak Academic Grant Agency

Number of participant	19 in total
Inclusion/Exclusion Criteria	The trial was the second part to a study Inclusion: non responders (less than 50% improvement) to 2 weeks of 20 micrograms intranasal desmopressin. Primary monosymptomatic NE, wet at least 3 nights per week, aged 5 to 18 years, no history of urological abnormalities, no day time incontinence, and no constipation.
Patient Characteristics	The mean age was 10.1 (sd 2.1) years, the mean number of wet nights per week before desmopressin treatment was 5.2 (sd 1.6) after desmopressin treatment the baseline mean number of wet nights per week was 4 (sd 1.2).
Recruitment	Attending enuresis outpatients clinic.
Setting	University Children's Hospital, Bratislava
Interventions/ Test/ Factor being investigated	Desmopressin 20 micrograms intranasal and 5 mg oxybutynin twice daily.
Comparisons	None.
Length of Study/ Follow-up	Not reported.
Outcome measures studied	Mean number of wet nights.
Results	2 weeks of treatment The mean number of wet nights after 2 weeks of treatment was 1.7 (sd 1.4) per week. Before treatment but after 2 weeks of desmopressin alone the mean number of wet nights per week was 4 (sd 1.2), $p < 0.001$.
Safety and adverse effects	Not reported
Does the study answer the question?	The study showed children resistant to desmopressin can respond to combined desmopressin and oxybutynin to see a reduction in the mean number of wet nights.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other studies
Directly applicable to guideline population?	Mean age of children 10.1 years
Internal Validity	Well covered

Serel TA;Perk H;Koyuncuoglu HR;Kosar A;Celik K;Deniz N;

Acupuncture therapy in the management of persistent primary nocturnal enuresis--preliminary results.[see comment]

Ref ID 576 2001

Study Type	Cohort	**Funding**	Not reported

Number of participant	50 patients
Inclusion/Exclusion Criteria	Inclusion: wet at least 3 nights a week, and failed treatment with desmopressin, imipramine or oxybutinin. Exclusion: history of UTI, bladder dysfunction, and other medical problems.
Patient Characteristics	33/50 were male, and the mean age was 10.3 years (range 9 to 18 years).
Recruitment	Seen between January 1997 and April 1999.
Setting	Turkey
Interventions/ Test/ Factor being investigated	Acupuncture.
Comparisons	No comparison.
Length of Study/ Follow-up	13 months follow up.
Outcome measures studied	Complete dryness
Results	Children had a 30 minute acupuncture treatment with disposable acupuncture needles on 10 consecutive days in a month. The study showed that within 6 months of starting treatment 43 out of 50 (86%) were completely dry, 2 out of 50 (4%) were 80% dry, 5 (10%) had relapsed and their therapy was intensified to produce a satisfactory response. After 13 months 40 patients were available for follow up. 35 of these were dry, 7 continued to have acupuncture of 2 days each month and were at least 80% dry. 3 patients had showed success and had started other treatments. There were no side effects.
Safety and adverse effects	None
Does the study answer the question?	The study showed that treatment with acupuncture could lead to complete dryness in children who had failed treatment with desmopressin, imipramine or oxybutinin.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other studies
Directly applicable to guideline population?	Children had an age range of 9 to 18 years
Internal Validity	Poorly addressed

Wikstrom S;Tapper J;

Are repeated desmopressin treatment attempts successful?

Ref ID 872 1997

Study Type Cohort **Funding** Not reported

Number of participant	96 patients
Inclusion/Exclusion Criteria	Inclusion: aged 5 to 8 years when first attempted treatment; no urological history, UTI, structural abnormality; no daytime incontinence; no urological, gastrointestinal, renal or cardiovascular disease; and have tried 3 previous treatments with the most recent being desmopressin.

Patient Characteristics	44 were male. The mean age was 6 years when children first tried treatment. The study age range was 7 to 18 years. 79% had a positive family history. 96% were wet 6 to 7 nights a week and 28% had only tried desmopressin. 71% had tried alarms and 58% had tried alarms with desmopressin.
Recruitment	Patients treated for primary NE between 1983 and 1994.
Setting	Childrens Hospital, University of Helsinki Finland
Interventions/ Test/ Factor being investigated	Intranasal desmopressin 20-40 micrograms at bedtime.
Comparisons	Comparisons were made between desmopressin alone, alternately or in combination with an alarm device.
Length of Study/ Follow-up	3 to 6 months
Outcome measures studied	Number of children who became dry
Results	Children were given 20 to 40 micro grams intranasal desmopressin at bedtime for 4 to 6 weeks. If patients responded the treatment was continued for 3 months using the dose the child responded at. If the child still dry after 3 months the treatment was continued for 3 to 6 months, but gradually reduced in dosage to 10 micro grams until the child was dry for 3 to 6 months. If the child did not respond to desmopressin after 4 to 6 weeks, children who had partially responded were given an alarm as well for 12 weeks, those who had not responded were taken off desmopressin and given an alarm instead for 12 weeks. In some children who failed treatment was stopped for 6 to 9 months and then started again. The study showed in children treated with desmopressin alone 14 out of 28 (50%) were cured, 10 out of 28 (36%) were dry when on desmopressin and 4 (14%) were still wet. In children treated with desmopressin and alarm 36 out of 68 (53%) were cured, 15 out of 68 (22%) were dry on treatment and 17 out of 68 (25%) were still wet. The study noted children over the age of 14 years thought desmopressin alone was the only acceptable form of treatment. The study did a sub group analysis on age to show that in children aged 7 to 8 years, 7 out of 10 (70%) were cured, 1 out of 10 (10%) were dry with desmopressin and 2 out of 10 (20%) were still wet. For children aged 9 to 13 years 35 out of 67 (52%) were cured, 15 out of 67 (22%) were dry with desmopressin and 17 out of 67 (25%) were still wet. For children aged 14 to 18 years, 8 out of 19 (42%) were cured, 9 out of 19 (47%) were dry with desmopressin and 2 out of 19 (11%) were still wet.
Safety and adverse effects	None reported
Does the study answer the question?	Study shows children who have not responded to desmopressin during the first 3 attempts of treatment for nocturnal enuresis may respond to another attempt of demsopressin but most chilldren require the addition of an alarm as they did not respond to desmopressin. The study noted children over the age of 14 years thought desmopressin alone was the only acceptable form of treatment.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other studies consider this treatment.
Directly applicable to guideline population?	Children had a mean age of 6 years.
Internal Validity	Adequately addressed

Question: In children and young people with nocturnal enuresis, how does patient or parent/carer choice over treatment intervention influence treatment outcomes?

Grading: 1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Lottmann H;Froeling F;Alloussi S;El-Radhi AS;Rittig S;Riis A;Persson BE;

A randomised comparison of oral desmopressin lyophilisate (MELT) and tablet formulations in children and adolescents with primary nocturnal enuresis

Ref ID 35 2007

Study Type Randomised Controlled Trial **Funding** Ferring pharmaceutical

Number of participant	221 in total
Inclusion/Exclusion Criteria	Inclusion: aged 5-15 years and primary NE. Exclusion: daytime urgency, frequency (>7 micturitions during day time), voiding postponement, infrequency (< 3 voiding during daytime), the use of non-pharmacological treatment for NE in previous 60 days, organic urological disease, day time wetting, diabetes insipidus, UTI, clinically significant renal, hepatic, gastrointestinal, pulmonary, cardiovascular, endocrine, or neurological disease.
Patient Characteristics	The mean age was 9.6 (SD 2.4) years and 71.6% were male. 34.4% were aged 5-8 years, 40.8% were aged 9-11 years 24.8% and were aged 12-15 years.
Recruitment	Not reported.
Setting	26 centres in Europe.
Interventions/ Test/ Factor being investigated	120 or 240 micrograms desmopresisn melt and 0.2 or 2X0.2 mg desmopresisn tablet.
Comparisons	Between desmopressin melts and desmopressin tablets.
Length of Study/ Follow-up	6 weeks
Outcome measures studied	Patient preference.
Results	26 centres in France, Germany, the Netherlands, UK, Sweden, Denmark, Norway, Finland and Iceland 3 weeks of each treatment. The study did ITT analysis. The study showed: 55.7% preferred the MELT formulation (95% CI: 48.7-62.7), compared with 44.3% who preferred the tablet formulation (95% CI: 37.5-51.3%; p=0.112). Treatment preference was strongly correlated with age (p=0.006), but not with treatment sequence (p=0.54) or dose (p=0.08). For patients aged <12 years (n=160), a statistically significant preference for the MELT formulation (60.6%; 95% CI: 52.6-68.2% and p=0.009) was reported. In the 5-8 years age group (n=72) and the 9-11 years (n=89), preference for MELT approached significance.
Safety and adverse effects	6 out of 109 patients in the melt desmopressin group had headaches compared to 0 out of 109 in the tablet desmopressin group 3 out of 109 patients in the melt desmopressin group had diarrhoa compared to 0 out of 109 in the tablet desmopressin group 3 out of 109 patients in the melt desmopressin group had viral gastroenteritis compared to 0 out of 109 in the tablet desmopressin group

Does the study answer the question?	The study showed: 55.7% preferred the MELT formulation, compared with 44.3% who preferred the tablet formulation. Treatment preference was strongly correlated with age, but not with treatment sequence or dose.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	
Directly applicable to guideline population?	Age range 5-15 years.
Internal Validity	cross over trial

Grading: 2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

Diaz SD;Chaviano AH;Maizels M;Yerkes EB;Cheng EY;Losavio J;Porten SP;Sullivan C;Zebold KF;Hagerty J;Kaplan WE;

Office Management of Pediatric Primary Nocturnal Enuresis: A Comparison of Physician Advised and Parent Chosen Alternative Treatment Outcomes

Ref ID 686 2007

Study Type Cohort **Funding** Not reported.

Number of participant	119 patients: n=76 in the physician treatment plan group and n=43 in the parent treatment plan group.
Inclusion/Exclusion Criteria	Inclusion: Primary NE, wetting at night during sleep during any 6 month interval without any known causative problem, more than 2 wet nights per week. Exclusion: coexisting anatomical urological problems (vesicouretral reflux or posterior urethral valves), dysfunctional elimination syndrome or urinary tract infection within a year before evaluation, and day-time wetting.
Patient Characteristics	85 males and 34 females. The mean age (sd) was 10 ± 3.
Recruitment	Not reported
Setting	Children's Memorial Hospital, Chicago Illinois USA
Interventions/ Test/ Factor being investigated	Physician treatment plan (n=76) Parent treatment plan (n=43) The physician treatment plans (76 patients) included an alarm, age appropriate incentives to reward dryness, an elimination diet to address possible underlying food sensitivities, oxybutinin to address small functional bladder capacity using a 3 times daily dose when functional bladder capacity is decreased according to the home diary, oxybutinin at a nightly dose (based on empirical clinical experience), desmopressin prescribed at a dose of 0.1mg at bedtime for children 8 to 13 years, and finally a bowel program if there was constipation. The parent chosen plans (43 children) included the personalised choice of single or combined use of a moisture alarm with age appropriate inducements, oxybutinin/desmopressin according to the presented dose scheme, an elimination diet and/or a bowel program.
Comparisons	Between physician and parent chosen plans.
Length of Study/ Follow-up	12 weeks.
Outcome measures studied	Differences in physician advised treatment and parent chosen treatment
Results	Time to Primary Nocturnal Enuresis (PNE) remission using physician advised treatment was significantly sooner than with parent chosen therapy (25th percentile 2 vs. 10 weeks). At the end of 12 weeks the probability of remission for the physician advised treatment group was significantly higher than for the parent chosen alternative treatment group (88% vs. 29%, p<0.00001).
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed physician advised treatment was more effective than parent chosen treatment.

Effect due to factor in study?	Yes.
Consistency of results with other studies?	Not clear.
Directly applicable to guideline population?	Children had a mean age of 10 (sd 3) years

Internal Validity

Question: What is the clinical and cost effectiveness of dry bed training for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Bennett GA;Walkden VJ;Curtis RH;Burns LE;Rees.J.;Gosling JA;

Pad-and-buzzer training, dry-bed training, and stop-start training in the treatment of primary nocturnal enuresis

Ref ID 360 1985

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant	40 in total: 9 in group A (pub and buzzer training), 12 in group B (stop start training), 10 in group C (dry bed training), 9 in group D (control-waiting list)
Inclusion/Exclusion Criteria	Inclusion: primary NE, not dry for more than 4 weeks, at least 6 wet night during 14 night baseline, and negligible day time wetting. Exclusion: encopresis, previous behavioural intervention, or gross psychopathology.
Patient Characteristics	63% were boys, the mean age was 8.5 (3.2 SD) years, and the age range was 5-12 years.
Recruitment	Referred from GP.
Setting	Treatment administered at home, Rochdale UK.
Interventions/ Test/ Factor being investigated	Group A: alarm (pad and buzzer) Group B: stop-start training (sphincter muscle exercises) Group C: DBT with alarm Group D: Control group - waiting list were given star chart after first dry night
Comparisons	Between treatment groups.
Length of Study/ Follow-up	0 months
Outcome measures studied	Numbers achieving 14 consecutive dry nights, mean number of wet nights at end of treatment, and drop outs.
Results	Dry bed training included: waking schedule, retention control training, positive practice and cleanliness training. Stop start training was sphincter muscle exercises 12 weeks treatment Results: Dry for 14 consecutive nights: In group A (alarm) 4 out of 9 children, became dry for 14 nights compared to 2 out of 12 in group B (stop start training), 5 out of 10 children, in group C (DBT with alarm) and 0 out of 9 children, in group D (control). Drop out: 32 children in total dropped out. In group A (alarm) 9 children, dropped out compared to 11 children in group B (stop start training) 10 children in group C (DBT with alarm) and 3 children in group D (control). All drop outs were after the first assessment before treatment was started Mean number of wet nights: The mean number of wet nights per week at end of treatment for the alarm group was 1 (SD 1.95) compared to 3.25 (SD 3.55) in the stop start training group, 1.4 (SD 4.65) for the dry bed training group and 5.15 (SD 1.5) for the no treatment alarm group.
Safety and adverse effects	None reported

Does the study answer the question?	Both alarm alone and DBT with alarm gave good results for achieving 14 dry nights (44% and 50%) and were more effective than the stop start training and no treatment. There was no significant difference in the number of drop outs in each group.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar results with other studies.
Directly applicable to guideline population?	Yes the age range was 5-12 years old.
Internal Validity	High drop out rate, unclear allocation concealment

Bollard J;Nettelbeck T;Roxbee L;

Dry-bed training for childhood bedwetting: a comparison of group with individually administered parent instruction

Ref ID 1754 1982

Study Type Randomised Controlled Trial **Funding**

Number of participant	30 in total: 10 in each group (Group A: DBT with alarm, Group B: DBT without alarm, and Group C: Waiting list)
Inclusion/Exclusion Criteria	Inclusion: wet at least 1 night a week, no underlying pathology, and no current treatment. Exclusion: organic causes of NE.
Patient Characteristics	18 were male. In group A (DBT and alarm) the mean age was 8 years and 5 months, the mean baseline wetting was 4.9 nights per week. In group B (DBT without alarm) the mean age was 9 years and 4 months, the mean baseline wetting was 5.0 nights per week. In group C (waiting list) the mean age was 9 years and 5 months, the mean baseline wetting was 5.3 nights per week.
Recruitment	Selected from outpatients list, Adelaide Children's Hospital, Australia.
Setting	Outpatients, Adelaide Children's Hospital.
Interventions/ Test/ Factor being investigated	Group A: DBT with alarm Group B: DBT without alarm Group C: Waiting list
Comparisons	Between treatment groups.
Length of Study/ Follow-up	3 months of follow up.
Outcome measures studied	Number of children achieving 14 consecutive dry nights, mean number of wet nights per week in the last week of treatment, and number of children relapsing or failed.
Results	Results from Cochrane review, presented in graphs in paper. Dry bed training included: waking schedule, retention control training, positive practice and cleanliness training and weekly meetings for parents and children. Treatment was until 14 consecutive dry nights were achieved or 8 weeks. 14 consecutive dry nights: In Group A (DBT with alarm) 9 out of 10 children achieved 14 consecutive dry nights compared to 2 out of 10 in Group B (DBT without alarm) and 0 out of 10 in Group C (waiting list). Mean number of wet nights per week in the last week of treatment: In Group A (DBT with alarm) the mean number of wet nights was 0.2 compared to

	3.25 in Group B (DBT without alarm) and 5.3 in Group C (waiting list). Number of children relapsing or failed: In Group A (DBT with alarm) 3 out of 10 children relapsed compared to 4 out of 10 in Group B (DBT without alarm) and there were no results for Group C (waiting list).
Safety and adverse effects	None reported.
Does the study answer the question?	The study shows children treated with DTB and alarm were more likely to achieve 14 consecutive dry nights and have fewer wet nights compared to children treated with DBT without alarm or no treatment.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar results with other studies comparing DBT without an alarm to a control group.
Directly applicable to guideline population?	Children had mean ages of 8 years and 5 months to 9 years and 5 months.
Internal Validity	Unclear allocation concealment

Nawaz S;Griffiths P;Tappin D;

Parent-administered modified dry-bed training for childhood nocturnal enuresis: Evidence for superiority over urine-alarm conditioning when delivery factors are controlled

Ref ID 54 2002

Study Type Randomised Controlled Trial **Funding** None reported.

Number of participant	36 in total: 12 in each of the three groups.
Inclusion/Exclusion Criteria	Inclusion: functional NE defined in DSM-IV (aged over 5 years, wet at least 2 times a week for 3 months, NE not due to primary medical or physiological pathology), aged between 7-12 years, attending a mainstream school, wetting 4 or more nights a week, no forseen domestic disruption during treatment time, and readiness to be involved in trial. Exclusion: diurnal enuresis or encopresis, bedwetting secondary to organic or psychiatric disorder or those unwilling to cooperate.
Patient Characteristics	In group A (DBT with alarm) the mean age was 9.93 years (1.81 SD), 50% were male, the mean baseline number of wet nights per week was 5.58 (1.31 SD) and the mean deprivation category (0-7) was 4.67 (2.15 SD). In group B (alarm) the mean age was 9.93 years (1.99 SD), 50% were male, the mean baseline number of wet nights per week was 5.50 (1.45 SD) and the mean deprivation category (0-7) was 4.75 (1.91 SD). In group C (control) the mean age was 9.84 years (1.84 SD), 50% were male, the mean baseline number of wet nights per week was 5.92 (1.08 SD) and the mean deprivation category (0-7) was 5.75 (1.71 SD).
Recruitment	From nine health centres (GPs, GP nurses, health visitors, community paediatricians).
Setting	Scotland, UK, treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: DBT with alarm Group B: alarm Grou C: control group - no treatment
Comparisons	Between groups A, B and C.
Length of Study/ Follow-up	6 months

Outcome measures studied	Numbers achieving 14 consecutive dry nights, mean number of wet nights, and numbers relapsing.
Results	Dry bed training included: waking schedule, retention control training, positive practice and cleanliness training. Patients were treated for 16 weeks or until dry Dry for 14 consecutive nights: In group A (DBT with alarm) 8 out of 12 children (67%) became dry for 14 nights compared to 3 out of 12 children (25%) in group B (alarm) and 1 out of 12 children (8%) in group C (control). This difference was significant ($p<0.01$). Mean number of wet nights: The mean number of wet nights per week at the end of treatment was 0.83 (sd 1.4) for children who had DBT with an alarm; for children who had an alarm the mean number of wet nights was 3.25 (sd 2.67) and for children in the control group (waiting list) the mean number of wet nights was 5 (sd 2.26). Relapse: At 3 month follow up, no children had relapsed. At 6 month follow up 1 out of 4 children in group A (DBT with alarm) and 1 out of 9 children in group B (alarm) had relapsed), both children were wetting 3 nights a week.
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that DBT with alarm was significantly more effective at achieving 14 dry nights compared to alarm alone and no treatment. The study also showed that DBT with alarm had a greater reduction in the mean number of wet nights compared to alarm alone and no treatment.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar results to other studies comparing DBT with alarm alarm to alarms and control group.
Directly applicable to guideline population?	The age range was 7-12 years.
Internal Validity	Unclear allocation concealment.

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Bollard J;Nettelbeck T;

A comparison of dry-bed training and standard urine-alarm conditioning treatment of childhood bedwetting

Ref ID 371 1981

Study Type	Randomised Controlled Trial	**Funding**	Research undertaken as part requirement for the degree of doctor of philosophy.

Number of participant	120 children: 82 males and 38 females. 20 in each of the 6 groups.
Inclusion/Exclusion Criteria	Inclusion: through medical examination, wet at least 1 night a week, and no other treatment during study. Exclusion: organic causes of NE.
Patient Characteristics	In group A (DBT with therapist in home) had a mean age of 9.3 years and 14 were male, and the baseline mean number of wet nights was 5.8. In group B (DBT with therapist in hospital) had a mean age of 8.11 years and 13 were male, and the baseline mean number of wet nights was 5.2. In group C (DBT with parents as therapist in home) had a mean age of 9.7 years and 16 were male, and the baseline mean number of wet nights was 6.0. In group D (DBT with parents as therapist in home without alarm) had a mean age of 8.6 years and 14 were male, and the baseline mean number of wet nights was 5.7. In group E (alarm) had a mean age of 8.8 years and 14 were male, and the baseline mean number of wet nights was 6.0. In group F (waiting list) had a mean age of 8.1 years and 1 were male, and the baseline mean number of wet nights was 4.7.
Recruitment	Children who were outpatients of the Adelaide Children's Hospital.
Setting	Outpatient service of Adelaide Children's Hospital
Interventions/ Test/ Factor being investigated	Group A: DBT with therapist in home Group B: DBT with therapist in hospital Group C: DBT with parents as therapist in home Group D: DBT with parents as therapist in home without alarm Group E: Alarm Group F: Waiting list
Comparisons	Between treatment groups.
Length of Study/ Follow-up	Followup at 3, 6 and 12 months.
Outcome measures studied	Number achieving 14 consecutive dry nights, mean number of wet nights per week at the end of week 20, and number of relapses.
Results	Dry bed training included: waking schedule, retention control training, positive practice and cleanliness training. Treatment was until patient achieved 14 consecutive dry nights or for 20 weeks. 14 consecutive dry nights: In group A (DBT with therapist in home) 20 out of 20 achieved 14 consecutive dry nights compared to 20 out of 20 in group B (DBT with therapist in hospital), 20 out of 20 in group C (DBT with parents as therapist in home), 5 out of 20 in group D (DBT with parents as therapist in home without alarm), 16 out of 20 in group E (alarm) and 2 out of 20 in group F (waiting list). Mean number of wet nights per week at the end of week 20: In group A (DBT with therapist in home) the mean number of wet nights was 0 compared to 0 in group B (DBT with therapist in hospital), 0 in group C (DBT with

	parents as therapist in home), 3.8 in group D (DBT with parents as therapist in home without alarm), 0.6 in group E (alarm) and 4.4 in group F (waiting list). Number of children who relapsed: In group A (DBT with therapist in home) 5 out of 20 relapsed compared to 6 out of 20 in group B (DBT with therapist in hospital), 4 out of 20 in group C (DBT with parents as therapist in home), 2 out of 5 in group D (DBT with parents as therapist in home without alarm), 6 out of 16 in group E (alarm) and 2 out of 2 in group F (waiting list).
Safety and adverse effects	None reported.
Does the study answer the question?	Study showed children treated wtith DBT and an alarm were more likely to achieve 14 consecutive dry nights and have fewer wet nights compared to children treated with DBT and no alarm, alarm or no treatment.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar results with other studies comparing DBT with an alarm to an alarm and control groups.
Directly applicable to guideline population?	Children had mean ages from 8.1 to 9.7.
Internal Validity	No blinding, unclear allocation concealment.

Keating JCJ;Butz RA;Burke E;Heimberg RG;

Dry bed training without a urine alarm: lack of effect of setting and therapist contact with child

Ref ID 467 1983

Study Type Randomised Controlled Trial **Funding**

Number of participant	30 in total: 7 in group A (DBT with hospital training for parents and child), 9 in group B (DBT with home training for parent and child), 7 in group C (DBT with hospital training for parents), 7 in group D (waiting list).
Inclusion/Exclusion Criteria	Include: diurnally continent, child must be able to follow intructions, wet at least 50% of nights Exclude: organic causes of NE, day time wetting.
Patient Characteristics	The mean age is 8.1 years, the age range was 4 to 14 years. Children were wet at least 50% of nights.
Recruitment	Newspaper adverts, referred from friends, paediatric urologist, and psychologist.
Setting	Hospital or home, Albany, USA.
Interventions/ Test/ Factor being investigated	Group A: DBT (no alarm) with hospital training for parents and child; 7 children Group B: DBT (no alarm) with home training for parent and child; 9 children Group C: DBT (no alarm) with hospital training for parents; 7 children Group D: waiting list; 7 children
Comparisons	Between treatment groups.
Length of Study/ Follow-up	5 months follow up.
Outcome measures studied	Number of children who achieved 14 consecutive dry nights, mean number of wet nights in the final week of treatment, number of children who relapsed.
Results	Dry bed training included: waking schedule, retention control training, positive practice and cleanliness training. Data taken from Cochrane as presented in graphical form in paper 5 weeks of treatment

	Number of children achieving 14 consecutive dry nights: In group A (DBT (no alarm) with hospital training for parents and child) 7 out of 7 children achieved 14 consecutive dry nights compared to 5 out of 9 in group B (DBT (no alarm) with home training for parent and child) and 6 out of 7 in group C (DBT (no alarm) with hospital training for parents). No results for group D (waiting list). Mean number of wet nights in final week of treatment: In group A (DBT (no alarm) with hospital training for parents and child) children had a mean number of wet nights of 2.7 compared to 2.5 in group B (DBT (no alarm) with home training for parent and child), 1.9 in group C (DBT (no alarm) with hospital training for parents) and 2 in group D (waiting list). Relapse: In group A (DBT (no alarm) with hospital training for parents and child) 2 out of 7 children relapsed compared to 2 out of 5 in group B (DBT (no alarm) with home training for parent and child) and 2 out of 6 in group C (DBT (no alarm) with hospital training for parents). No results for group D (waiting list).
Safety and adverse effects	None reported
Does the study answer the question?	Study shows children treated with dry bed training where training is given in a hospital were more likely to achieve 14 conseuctive dry nights compared to no treatment or training at home. Children who had DBT where only parents had training in a hosptial had fewer wet nights per week at the end of treatment compared to other dry bed training or no treatment.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Study shows similar results to other studies comparing DBT with an alarm and DBT without an alarm and waiting list group.
Directly applicable to guideline population?	Children had an age range of 4 to 14 years.
Internal Validity	No blinding, unclear allocation concealment.

Question: What is the clinical and cost effectiveness of bladder training / retention control training for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Hamano S;Yamanishi T;Igarashi T;Ito H;Murakami S;

Functional bladder capacity as predictor of response to desmopressin and retention control training in monosymptomatic nocturnal enuresis

Ref ID 1413 2000

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	114 in total 54 in group A (desmopressin), 60 in group B (retention control training)
Inclusion/Exclusion Criteria	Inclusion: primary monosymptomatic NE, aged 5 to 15 years, and wet at least 4 times a week Exclusion: organic causes of NE or UTI.
Patient Characteristics	88 out of 114 were male. In group A (desmopressin) the mean age was 9.2 (sd 2.2) years. The mean baseline wetting was 6.8 (sd 0.7) nights a week, 88.9% were wet every night and 67% (sd 24) had normal bladder capacity. In group B (retention control training) the mean age was 9.4 (sd 2.3) years. The mean baseline wetting was 6.7 (sd 0.9) nights a week, 85% were wet every night and 59% (sd 22) had normal bladder capacity.
Recruitment	Presented to clinic between April 1993 and October 1998.
Setting	Chiba, Japan
Interventions/ Test/ Factor being investigated	Group A: desmopressin 5 micrograms intranasally increasing in 5 microgram increments up to 20 micrograms if no response Group B: retention control training where children were asked once a day to avoid voiding for a long as possible to expand bladder capacity. The amount voided was recorded. Both groups also had fluid restriction at bedtime.
Comparisons	Between groups A and B
Length of Study/ Follow-up	2 weeks of follow up
Outcome measures studied	Number of children who achieved 14 consecutive dry nights. Adverse events.
Results	Treatment was for 12 weeks Number of children who achieved 14 consecutive dry nights: In group A (desmopressin) 21 out of 54 children achieved 14 consecutive dry nights compared to 14 out of 60 in group B (retention control training) Adverse events: In group A (desmopressin) 2 out of 54 children had nasal discomfort, no patients in group B (retention control training) had nasal discomfort. Relapse rates: In group A (desmopressin) 17 out of 21 children relapsed compared to 5 out fo 14 patients in group B (retention control training).
Safety and adverse effects	In group A (desmopressin) 2 out of 54 children had nasal discomfort and no patients in group B (retention control training) had nasal discomfort.
Does the study answer the question?	The study showed that more children treated with desmopressin achieved 14 consecutive dry nights compared to children treated with retention control training.
Effect due to factor in study?	Yes

Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Children were aged 5 to 15 years.
Internal Validity	Unclear allocation concealment

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Bennett GA;Walkden VJ;Curtis RH;Burns LE;Rees.J.;Gosling JA;

Pad-and-buzzer training, dry-bed training, and stop-start training in the treatment of primary nocturnal enuresis

Ref ID 360 1985

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant	40 in total: 9 in group A (pub and buzzer training), 12 in group B (stop start training), 10 in group C (dry bed training), 9 in group D (control-waiting list)
Inclusion/Exclusion Criteria	Inclusion: primary NE, not dry for more than 4 weeks, at least 6 wet night during 14 night baseline, negligible day time wetting. Exclusion: encopresis, previous behavioural intervention, or gross psychopathology.
Patient Characteristics	63% were boys, th mean age was 8.5 (3.2 SD) years, and the age range was 5-12 years.
Recruitment	Referred from GP.
Setting	Treated at home, Rochdale UK.
Interventions/ Test/ Factor being investigated	Group A: alarm (pad and buzzer) Group B: stop-start training (sphincter muscle exercises) Group C: DBT with alarm Group D: Control group - waiting list were given star chart after first dry night
Comparisons	Between treatment groups.
Length of Study/ Follow-up	0 months
Outcome measures studied	14 consecutive dry nights, mean dry nights at follow up, drop out
Results	12 weeks treatment Results: Dry for 14 consecutive nights: In group A (alarm) 4 out of 9 children, became dry for 14 nights compared to 2 out of 12 in group B (stop startr trinaing), 5 out of 10 children, in group C (DBT with alarm) and 0 out of 9 children, in group D (control). Drop out: 32 children in total dropped out. In group A (alarm) 9 out of 18 children, dropped out compared to 11 out of 21 children in group B (stop start training) 10 children in group C (DBT with alarm) and 3 children in group D (control).
Safety and adverse effects	None reported
Does the study answer the question?	Both alarm alone and DBT with alarm gave good results for achieving 14 dry nights (44% and 50%) and were more effective than the stop start training and no treatment. There was no significant difference in the number of drop outs in each group.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Yes the age range was 5-12 years old.

Internal Validity	Unclear allocation concealment

Harris LS;Purohit AP;

Bladder training and enuresis: a controlled trial

Ref ID 499 1977

Study Type	Randomised Controlled Trial	**Funding**	Not reported.

Number of participant	18 in total, 9 in Group A (retention control training), 9 in Group B (waiting list).
Inclusion/Exclusion Criteria	Inclusion: recruited form newspaper adverts, wet at least 1 night a week, aged 5 to 13 years. Exclusion: organic causes of NE, day time wetting, mental deficiency, urinary infection, diabetes, anatomical defects, or current treatment for NE.
Patient Characteristics	In Group A (retention control training) 5 out of 9 were male, the mean age was 9.2 years, the baseline wetting was 3.2 nights a week. In Group B (waiting list) 7 out of 9 were male, the mean age was 8.8 years, the baseline wetting was 5 nights a week.
Recruitment	Newspaper advert.
Setting	Queen's University, Kingston, Ontario, Canada
Interventions/ Test/ Factor being investigated	Group A: retention control training. 5 nights in a camp, then 30 days with parents. Retention control training - on the first day the child was asked to drink fluid and the time to void was recorded as was the volume voided. After this children were encouraged to hold for longer, and were given 1 point for each extra 2 minutes held. The child was then taught that the longer they held the more urine the passed. Once the child understood this they were given points based on the amount of urine passed. Points were exchanged for toys and games etc. Group B: waiting list
Comparisons	Between treatment groups.
Length of Study/ Follow-up	9 weeks of follow up.
Outcome measures studied	Mean number of wet nights at the end of treatment.
Results	Mean number of wet nights per week at the end of treatment: In Group A (retention control training) the mean number of wet nights per week was 2.6 compared to 5 nights in Group B (waiting list).
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that children treated with retention control training had fewer wet nights per week after treatment compared to those in the waiting list group.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged 5-13 years.
Internal Validity	Unclear allocation concealment and blinding

Iester A;Marchesi A;Cohen A;Iester M;Bagnasco F;Bonelli R;

Functional enuresis: pharmacological versus behavioral treatment

Ref ID 384 1991

Study Type	Randomised Controlled Trial	**Funding**	Not reported

Number of participant	168 in total, 36 in group A (imipramine), 36 in group B (3 step program) and 96 in group C (counselling, 3 step program and education)
Inclusion/Exclusion Criteria	Inclusion: functional enuresis. Exclusion: organic causes of NE or emotional disturbance.
Patient Characteristics	The age range was 6 to 11
Recruitment	Patients seen between 1979 and 1988.
Setting	Genoa University, Genova, Italy
Interventions/ Test/ Factor being investigated	Group A: imipramine for 6 weeks 0.9-1.5mg/kg (maximum dosage 50 mg). Group B: 3 step program of reassurance to parents, bladder control training and waking with an alarm clock before micturition, and parental involvement. Group C: motivational therapy and 3 step program.
Comparisons	Between treatment groups
Length of Study/ Follow-up	12 month follow up.
Outcome measures studied	Number of children who achieved 14 consecutive dry nights. Relapse after 12 months.
Results	Children in the bladder training group took part in a three step program which was 1) reassurance to the parents and tried to encourage the child; 2) bladder retention training (drink more during the morning and afternoon, reduce the number of times voided during the day, trying to hold for at least 8 hours and interrupt voiding – stop start training) and behaviour training (drink as little as possible after 7 pm, urinate before going to bed and wake up once or twice using an alarm clock); 3) parents were involved in the treatment to help the child practice and avoid family conflicts. Children in the motivation therapy group had the 3 step program as described and motivational therapy where child, in a group, discussed their problems with a psychiatrist. Treatment was for 6 months. Number of children who achieved 14 consecutive dry nights: In group A (imipramine) 14 out of 36 achieved 14 consecutive dry nights compared to 24 out of 36 in group B (3 step program) and 81 out of 96 in group C (counselling, 3 step program and education). Relapse after 12 months In group A (imipramine) 2 out of 14 relapsed compared to 2 out of 24 in group B (3 step program) and 3 out of 81 in group C (counselling, 3 step program and education).
Safety and adverse effects	None reported
Does the study answer the question?	The study showed that more children treated with counselling, 3 step program and education achieved 14 consecutive dry nights compared to imipramine or the 3 step program.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies

Directly applicable to guideline population?	Children were aged 6 to 11 years.
Internal Validity	Unclear allocation concealment

Kahan E;Morel D;Amir J;Zelcer C;

A controlled trial of desmopressin and behavioral therapy for nocturnal enuresis

Ref ID 251 1998

Study Type Randomised Controlled Trial **Funding** Lapidot laboratories.

Number of participant	228 in total, 70 in group A (desmopressin and behaviour), 75 in group B (placebo and behaviour) and 76 in group C (desmopressin)
Inclusion/Exclusion Criteria	Inclusion: primary NE, wet at least 2 times a week, and aged 8-14 years. Exclusion: previous treatment, other physical disorders, previous traumatic life events, psychiatric disorders, or abnormal laboratory findings.
Patient Characteristics	In group A (desmopressin and behaviour) the mean baseline wetting was 5.1 (sd 2.1) nights a week, in group B (placebo and behaviour) the mean wetting was 5.5 (sd 1.8) and in group C (desmopressin) it was 5.8 (sd 1.6).
Recruitment	Seen at primary care clinic.
Setting	Golda Medical Center, General Sick Fund, Israel.
Interventions/ Test/ Factor being investigated	Group A: desmopressin (20 micrograms intranasally) and behaviour therapy of ensuring the child knows that NE is not due to “powerful external forces” but a psychologic mechanism. Group B: placebo and behaviour therapy Group C: desmopressin
Comparisons	Between treatment groups.
Length of Study/ Follow-up	2 months follow up.
Outcome measures studied	Mean number of wet nights per week at the end of treatment and at follow up, the number of children who achieved 14 consecutive dry nights, relapses, and adverse events.
Results	The child was made aware that “the problem is not a consequence of powerful external forces, but a psychologic mechanism which requires conscious self-control and that can be solved by taking responsibility”. The child was then taught sphincter muscle exercises. The child was also asked to go to bed earlier and drink less than usual, the child was also taught general physical exercises. Treatment was for 8 weeks Number of children who achieved 14 consecutive dry nights In group A (desmopressin and behaviour) 22 out of 70 achieved 14 consecutive dry nights compared to 12 out of 75 in group B (placebo and behaviour) and 31 out of 76 in group C (desmopressin) Mean number of wet nights per week at the end of treatment In group A (desmopressin and behaviour 70 children) the mean number of wet nights per week was 3.0 (sd 2.0) compared to 3.3 (sd 2.2) in group B (placebo and behaviour 75 children) and 4.5 (sd 1.8) in group C (desmopressin 76 children). Mean number of wet nights per week at follow up In group A (desmopressin and behaviour 70 children) the mean number of wet nights per week was 2.6 (sd 1.7) compared to 3.0 (sd 2.0) in group B (placebo and behaviour 74 children) and 4.7 (sd 1.8) in group C (desmopressin 76 children). Adverse events: In group A (desmopressin and behaviour) 5 out of 70 had nasal itch compared to 1 out of 75 in group B (placebo and behaviour) and 4 out of 76 in group C

	(desmopressin). Drop outs: In group A (desmopressin and behaviour) 6 out of 70 dropped out compared to 1 out of 75 in group B (placebo and behaviour) and 0 out of 76 in group C (desmopressin). Number of children who relapsed: In group A 18 out of 22 children relapsed compared to 6 out of 12 in group B and 28 out of 31 in group C.
Safety and adverse effects	In group A (desmopressin and behaviour) 5 out of 70 had nasal itch compared to 1 out of 75 in group B (placebo and behaviour) and 4 out of 76 in group C (desmopressin).
Does the study answer the question?	The study shows more children treated with desmopressin and behaviour or desmoropessin alone had successful treatment compared to chidlren treated with placebo and behaviour.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	
Directly applicable to guideline population?	Children were aged 8-14 years
Internal Validity	Unclear allocation concealment and blinding

Question: What is the clinical and cost effectiveness of lifting and/or waking for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Bhatia MS;Dhar NK;Rai S;Malik SC;

Enuresis: an analysis of 82 cases

Ref ID 1738 1990

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	60 in tota:l 20 in group A (placebo and restriction of fluid with avoiding punishment), 20 in group B (imipramine) and 20 in group C (imipramine and restriction of fluid with avoiding punishment). The groups were matched for age and sex. There were originally 82 children. 22 dropped out due to not being seen at follow up and were not included in the results.
Inclusion/Exclusion Criteria	Inclusion: aged 4 to 12 years, NE or diurnal enuresis or daytime wetting. Exclusion: organic causes of NE.
Patient Characteristics	39 out of 60 were male. 15 children were aged 4-5 years, 30 children were aged 6-8 years and 15 children were aged 9-12 years. 63.4% had NE only, 29.3% had both NE and diurnal enuresis 7.3% had diurnal enuresis only. 21.9% had a family history of enuresis, 50% wet daily, 31.6% wet 1-3 times a week, 12.3% wet once a month and 6.1% wet occasionally.
Recruitment	Not reported.
Setting	Delhi, India.
Interventions/ Test/ Factor being investigated	Group A: placebo and restriction of fluid with avoiding punishment and waking. Group B: Imipramine 10 mg for children aged 3-6 years, 25 mg for children aged over 6 years. The dose was doubled after 2 weeks if there was no improvement. Group C: imipramine and restriction of fluid with avoiding punishment and waking
Comparisons	Between treatment groups.
Length of Study/ Follow-up	6 months follow up.
Outcome measures studied	Number of children who achieved 14 consecutive dry nights.
Results	Fluid restriction was described as “restricting fluids in the evening” as well as avoiding punitive attitude of the parents and waking the child one hour after sleep. Treatment was for 6 weeks Number of children who achieved 14 consecutive dry nights: In group A (behaviour and placebo) 4 out of 20 children achieved 14 consecutive dry nights compared to 12 out of 20 in group B (imipramine) and 18 out of 20 in group C (imipramine and behaviour). Drop outs 22 in total due to being unavailable for follow up.
Safety and adverse effects	Not reported.
Does the study answer the question?	The study showed that children treated with imipramine and the behaviour intervention or imipramine alone were more likely to achieve 14 consecutive dry nights compared to children treated with a placebo and behaviour intervention.
Effect due to factor in study?	Yes.

Consistency of results with other studies?	No other studies compared fluid restriction.
Directly applicable to guideline population?	Children were aged 4 to 12 years.
Internal Validity	Unclear allocation concealment

El Anany FG;Maghraby HA;El-Din S;bdel-Moneim AM;

Primary nocturnal enuresis: A new approach to conditioning treatment

Ref ID 1146 1999

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	125 in total, 70 in Group A, 55 in Group B
Inclusion/Exclusion Criteria	Inclusion: wet at least 3 nights a week, and aged over 7 years. Exclusion: organic causes of NE, secondary NE, polysymptomatic, Urinary, structural or clinical neurological abnormalities.
Patient Characteristics	In Group A 46 out of 70 were boys, the mean age was 13.23 (sd 3.75) years, and the age range was 7-21 years. The baseline wetting was 5.24 (sd 1.22) wet nights per week. In Group B 32 out of 55 were boys, the mean age was 12.49 (sd 3.62) years, and the age range was 7-19 years. The baseline wetting was 5.13 (sd 1.17) nights a week.
Recruitment	Not reported.
Setting	Egypt
Interventions/ Test/ Factor being investigated	Group A: clock alarm set while still expected to be dry i.e. before child usually wets Group B: clock alarm set 2-3 hours after child goes to bed Both groups also had fluid restriction for 2 hours before going to bed
Comparisons	Between treatment groups.
Length of Study/ Follow-up	6 months
Outcome measures studied	Dry for 14 consecutive nights (success) in first month, after 3 months, and at 6 months follow up.
Results	Treatment was for 4 months In Group A (alarm set before child wets) 54 out of 70 children became dry compared to 34 out of 55 in Group B (alarm set 2-3 hours after bed) in the first month of treatment. In Group A (alarm set before child wets) 8 out of 54 children relapsed at 3 months compared to 3 out of 34 in Group B (alarm set 2-3 hours after bed). In Group A (alarm set before child wets) 13 out of 54 children were relapsed at 6 months compared to 5 out of 34 in Group B (alarm set 2-3 hours after bed). There was a high drop out rate of 64 children after the first month.
Safety and adverse effects	None.
Does the study answer the question?	The study evaulates two beneifit of waking children at different times.
Effect due to factor in study?	Yes.

Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	The study evaluates children aged 7 to 21 years. However the mean ages are 12 and 13 years.
Internal Validity	Unclear allocation concealment

Fournier JP;Garfinkel BD;Bond A;Beauchesne H;Shapiro SK;

Pharmacological and behavioral management of enuresis

Ref ID 346 1987

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	64 in total, 8 in each group
Inclusion/Exclusion Criteria	Inclusion: aged between 5 and 14 years, no history of UTI or disease, no physical or neurological disorder, at least 2 wet nights a week for previous 6 months, no treatment in previous 3 months, no significant cognitive impairment or mental retardation, imformed consent to random allocation of treatment
Patient Characteristics	73% were boys, the mean age was 8.5 years, 70% of children lived with their biological parent, 14% lived with a single parent, 83% were either the oldest or second eldest child in their family, 77% had had a first degree relative with enuresis and 61% had another relative with enuresis
Recruitment	Newspaper adverts and referred from paediatricians
Setting	at home, Montreal Canada
Interventions/ Test/ Factor being investigated	Group A: Imipramine Group B: Alarm Group C: Placebo Group D: Random waking Group E: Alarm with imipramine The paper also considered alarm with a placebo, random waking with a placebo and imipramine with random waking however there were no results presented for these groups.
Comparisons	Between treatment groups
Length of Study/ Follow-up	3 months
Outcome measures studied	Change in number of wet nights, drop out
Results	Random waking was the parent waking the child any time before midnight. 6 weeks treatment There were 8 patients in each group In group A (imipramine) the mean number of wet nights was 1.9 compared to 2.5 in group B (alarm), 5 in group C (placebo), 3.3 in group D (random waking) and 1 in group E (alarm with imipramine) Drop out: In total 4 boys dropped out due to side-effects or non-compliance and 1 girl dropped out due to having a UTI
Safety and adverse effects	None reported

Does the study answer the question?	The study showed that imipramine had a fasted effect than the other treatments, however at 4 weeks the most effective treatments were alarm, alarm with imipramine and imipramine alone. At the 3 month follow up the most sucessful treatments were alarm and imipramine.
Effect due to factor in study?	Yes (NB there is a 15% spontaneous cure rate)
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	children were aged 5 - 14 years old
Internal Validity	Unclear allocation concealment

Iester A;Marchesi A;Cohen A;Iester M;Bagnasco F;Bonelli R;

Functional enuresis: pharmacological versus behavioral treatment

Ref ID 384 1991

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	168 in total: 36 in group A (imipramine), 36 in group B (3 step program) and 96 in group C (counselling, 3 step program and education).
Inclusion/Exclusion Criteria	Inclusion: functional enuresis. Exclusion: organic causes of NE, or emotional disturbance.
Patient Characteristics	The age range was 6 to 11.
Recruitment	Patients seen between 1979 and 1988.
Setting	Genoa University, Genova, Italy.
Interventions/ Test/ Factor being investigated	Group A: imipramine for 6 weeks 0.9-1.5mg/kg maximum dosage 50 mg Group B: 3 step program of reassurance to parents, bladder control training and waking with an alarm clock before micturition, parental involvement Group C: motivational therapy and 3 step program
Comparisons	Between treatment groups.
Length of Study/ Follow-up	12 month follow up.
Outcome measures studied	Number of children who achieved 14 consecutive dry nights, and relapse after 12 months.
Results	Children in the bladder training group took part in a three step program which consisted of 1) reassurance to the parents and encouragement to the child; 2) bladder retention training (drink more during the morning and afternoon, reduce the number of times voided during the day, trying to hold for at least 8 hours and interrupt voiding – stop start training) and behaviour training (drink as little as possible after 7 pm, urinate bedfore going to bed and wake up once or twice using an alarm clock); 3) parents were involved in the treatment to help the child practice and avoid family conflicts. Children in the motivation therapy group had the 3 step program as described and motivational therapy where child, in a group, discussed their problems with a psychiatrist. Treatment was for 6 months Number of children who achieved 14 consecutive dry nights

	In group A (imipramine) 14 out of 36 achieved 14 consecutive dry nights compared to 24 out of 36 in group B (3 step program) and 81 out of 96 in group C (counselling, 3 step program and education). Relapse after 12 months In group A (imipramine) 2 out of 14 relapsed compared to 2 out of 24 in group B (3 step program) and 3 out of 81 in group C (counselling, 3 step program and education).
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that more children treated with counselling, 3 step program and education achieved 14 consecutive dry nights compared to imipramine or the 3 step program alone.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged 6 to 11 years.
Internal Validity	Unclear allocation concealment

Turner RK;Young GC;Rachman S;

Treatment of nocturnal enuresis by conditioning techniques

Ref ID 164 1970

Study Type Randomised Controlled Trial **Funding** The Bethlem-Maudsley Research Fund

Number of participant	115 in total:81 in groups A, B, 12and C (conditioning treatment), 34 in groups D and E (controls)
Inclusion/Exclusion Criteria	Inclusion: aged between 4-15 years, and wet at least 3 times a week. Exclusion: organic pathology, adverse home conditions with contra-indicated treatment by this method, having tried conditioning treatment in the previous year
Patient Characteristics	The mean age was 7.5 (2.6 SD) years (10 children were aged over 10 years), 69.6% were boys, 90% had primary NE, 65.2% were wet every night, 7% were wet 6 times a week, 5.1% were wet 5 times a week, 15.7% were wet 4 times a week and 7% were wet 3 times a week. 68.7% had a family history of NE.
Recruitment	Referred from school medical officer or brought for treatment by parents to 2 clinics in east London, UK.
Setting	London, UK, and treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm with continuous signal Group B: alarm with twin signal Group C: alarm with intermittent twin signal (after first 2 weeks alarm was sometimes diconnected) Group D: random waking Group E: placebo tablet
Comparisons	Between groups A, B, C, D and E
Length of Study/ Follow-up	3 years
Outcome measures studied	Number of children achieving 14 consecutive dry nights.

Results	Random waking consisted of the parents being given a chart with random times on it when the child should be woken. 14 consecutive dry nights: 3 out of 15 in group A (alarm with continuous signal) achieved 14 nights dry compared to 2 out of 15 in group B (alarm with twin signal), 1 out of 15 in group D (random waking) and 4 out of 17 in group E (placebo). The study states these differences are not significant. Drop-out: From groups A, B and C: 39 patients dropped out From groups D and E: 1 patient dropped out These drop outs are due to non-compliance with treatment procedure. The study did not report the results for group C
Safety and adverse effects	None reported.
Does the study answer the question?	The study reported low rates of success of achieving 14 consecutive dry nights, with placebo patients having the highest results of 24%, the alarm with continuous signal (20%), alarm with twin signal (13%) and random waking (6%). The differences were not significant.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Age range was 4-15 years.
Internal Validity	Unclear allocation concealment

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Baker BL;

Symptom treatment and symptom substitution in enuresis

Ref ID 340 1969

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant	30 patients in total
Inclusion/Exclusion Criteria	Patients were excluded if there was an organic cause of wetting
Patient Characteristics	67% were boys. The median age was 8 years with a range of 6-12 years. 4 patients had secondary enuresis. More than half the patients wet every night
Recruitment	From newpaper adverts
Setting	At home, USA
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: waking using an alarm clock and star chart Group C: waiting list group
Comparisons	Between treatment groups
Length of Study/ Follow-up	no follow up
Outcome measures studied	Change in number of wet nights Self image questionnaire
Results	Star charts were used to keep a record of the child's progress and the child was woken at a set time every night (chosen at start of trial to be before when the child usually wets), once the child was dry for several nights they were not woken for a week, if dry during the week the parents were told if the child wets wake them for the two following nights 10 weeks treatment 10 patients in each group Mean number of wet nights per week in the last 3 weeks of treatment: In group A (alarm) the mean number of wet nights was 1.8, in group B (waking and star chart) the mean number of wet nights was 3.1 and in group C (waiting list) the mean number of wet nights was 5.9. number of chidlren who achieved 14 consective dry nights: in the alarm group 11 out of 14 children had 14 consecutive dry ngihts comapred to 2 out of 14 in the waking group and 0 out of 14 in the control group. Relapsed: In total, 4 patients relapsed
Safety and adverse effects	None reported
Does the study answer the question?	Significantly more children became dry for 14 nights when treated with alarm therapy compared to no treatment (79% compared to 0%).
Effect due to factor in study?	Yes (NB there is a 15% sponatnoeus cure rate)

Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	The age range was 6-12 years
Internal Validity	Unclear allocation concealment and blinding

Question: What is the clinical and cost effectiveness of fluid and dietary advice for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Bhatia MS;Dhar NK;Rai S;Malik SC;

Enuresis: an analysis of 82 cases

Ref ID 1738 1990

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	#Deleted
Inclusion/Exclusion Criteria	Inclusion: aged 4 to 12 years, NE or diurnal enuresis or daytime wetting. Exclusion: organic causes of NE.
Patient Characteristics	#Deleted
Recruitment	Not reported.
Setting	Delhi, India.
Interventions/ Test/ Factor being investigated	Group A: placebo and restriction of fluid with avoiding punishment and waking Group B: Imipramine 10 mg for children aged 3-6 years, 25 mg for children aged over 6 years. The dose was doubled after 2 weeks if there was no improvement Group C: imipramine and restriction of fluid with avoiding punishment and waking.
Comparisons	Between treatment groups.
Length of Study/ Follow-up	6 months follow up
Outcome measures studied	Number of children who achieved 14 consecutive dry nights.
Results	Fluid restriction was described as “restricting fluids in the evening” as well as avoiding punitive attitude of the parents and waking the child one hour after sleep. Treatment was for 6 weeks Number of children who achieved 14 consecutive dry nights: In group A (behaviour and placebo) 4 out of 20 children achieved 14 consecutive dry nights compared to 12 out of 20 in group B (imipramine) and 18 out of 20 in group C (imipramine and behaviour) Drop outs 22 in total due to being unavailable for follow up.
Safety and adverse effects	Not reported
Does the study answer the question?	The study showed that children treated with imipramine and the behaviour intervention or imipramine alone were more likely to achieve 14 consecutive dry nights compared to children treated with a placebo and behaviour intervention.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other studies compared fluid restriction.
Directly applicable to guideline population?	Children were aged 4 to 12 years.
Internal Validity	Unclear allocation concealment

McKendry JB;Stewart DA;Khanna F;Netley C;

Primary enuresis: relative success of three methods of treatment

Ref ID 350 1975

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	222 in total: 73 in group A (diet restriction), 74 in group B (imipramine) and 75 in detector.
Inclusion/Exclusion Criteria	Inclusion: aged over 5 years. Exclusion: organic causes of NE.
Patient Characteristics	The mean age was 9 years and age range was 5 to 17 years. Some children (“a few”) had diurnal wetting. In group A (diet restriction) the mean baseline wetting was 83.4%, and in group B (imipramine) the mean baseline wetting was 82.3%.
Recruitment	Not reported.
Setting	The Hospital for Sick Children, Toronto, Canada.
Interventions/ Test/ Factor being investigated	Group A: diet restriction (the diet contained no milk, butter, cheese, eggs, citrus fruit juices, tomato, coca or chocolate. Instead apple juice, ginger ale and water were used as fluid substitutes Group B: 10mg Imipramine increasing to 40mg for children aged under 10 years and 60mg for children older than 10 years if needed The study also considered an alarm which gave the child an electric shock, this is not normal clinical practice and therefore the treatment group was not included in the review.
Comparisons	Between group A and group B.
Length of Study/ Follow-up	Group A (diet restriction) had 3 months follow up and group B (imipramine) had 19 month follow up.
Outcome measures studied	Number of children who achieved 14 consecutive dry nights after treatment and at follow up, greater than 50% improvement in the number of dry nights after treatment and at follow up, drop outs, and adverse events.
Results	Number of children who achieved 14 consecutive dry nights: In group A 1 out of 64 achieved 14 consecutive dry nights compared to 13 out of 62 in group B (imipramine) Greater than 50% improvement in the number of dry nights: In group A 34 out of 64 achieved a greater than 50% improvement in the number of dry nights compared to 28 out of 62 in group B (imipramine) Number of children who achieved 14 consecutive dry nights at follow up: In group A 1 out of 1 achieved 14 consecutive dry nights compared to 19 out of 34 in group B (imipramine) Greater than 50% improvement in the number of dry nights at follow up: In group A 0 out of 1 achieved a greater than 50% improvement in the number of dry nights compared to 8 out of 34 in group B (imipramine) Drop outs: In group A (diet restriction) 9 out of 73 dropped out compared to 12 out of 74 in group B (imipramine) Adverse events: In group A (diet restriction) 2 out of 12 children became aggressive In group B (imipramine)3 out of 16 children had headaches, abdominal pain or fatigue
Safety and adverse effects	In group A (diet restriction) 2 out of 12 children became aggressive. In group B (imipramine)3 out of 16 children had headaches, abdominal pain or fatigue.

Does the study answer the question?	The study showed that children treated with imipramine were more likely to become dry or have an 50-80% improvement in the number of dry nights compared to children treated with dietary restriction. Children from Group A had a shorter followup as after 3 months parents switched treatment due to the diet being unsuccessful.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other studies comparing diet restriction to imipramine.
Directly applicable to guideline population?	Children were aged 5 to 17 years.
Internal Validity	Unclear allocation concealment

Question: What is the clinical and cost effectiveness of star charts and other reward systems for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Bennett GA;Walkden VJ;Curtis RH;Burns LE;Rees.J.;Gosling JA;

Pad-and-buzzer training, dry-bed training, and stop-start training in the treatment of primary nocturnal enuresis

Ref ID 360 1985

Study Type Randomised Controlled Trial **Funding** None reported.

Number of participant	40 in total: 9 in group A (pub and buzzer training), 12 in group B (stop start training), 10 in group C (dry bed training), 9 in group D (control-waiting list)
Inclusion/Exclusion Criteria	Inclusion: primary NE, not dry for more than 4 weeks, at least 6 wet nights during 14 night baseline period, and negligble day time wetting. Exclusion: encopresis, previous behavioural intervention, or gross psychopathology.
Patient Characteristics	63% were boys, the mean age was 8.5 (3.2 SD) years, and the age range was 5-12 years.
Recruitment	Referred from GP.
Setting	Treatment administered at home, Rochdale UK
Interventions/ Test/ Factor being investigated	Group A: alarm (pad and buzzer) Group B: stop-start training (sphincter muscle exercises) Group C: DBT with alarm Group D: Control group - waiting list were given star chart after first dry night
Comparisons	Between treatment groups.
Length of Study/ Follow-up	12 weeks.
Outcome measures studied	14 consecutive dry nights, mean dry nights at follow up, drop out
Results	12 weeks treatment Results: Dry for 14 consecutive nights: In group A (alarm) 4 out of 9 children became dry for 14 nights compared to 2 out of 12 in group B (stop start training), 5 out of 10 children, in group C (DBT with alarm) and 0 out of 9 children, in group D (star chart). Drop out: 32 children in total dropped out. In group A (alarm) 9 children, dropped out compared to 11 children in group B stop start training) 10 children in group C (DBT with alarm) and 3 children in group D (star chart). Change in mean number of wet nights: The mean number of wet nights per week at end of treatment for the alarm group was 1 (SD 1.95) compared to 3.25 (SD 2.60) in stop start training group, 1.4 (SD 1.8) for the dry bed training group and 5.15 (SD 1.5) for the star chart alarm group.
Safety and adverse effects	None reported.
Does the study answer the question?	Both alarm alone and DBT with alarm gave good results for achieving 14 dry nights (44% and 50%) and were more effective than the stop start training and no treatment. There was no significant difference in the number of drop outs in each group.
Effect due to factor in study?	Yes.

Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Yes the age range was 5-12 years old.
Internal Validity	Unclear allocation concealment

Ronen T;Wozner Y;Rahav G;

Cognitive intervention in enuresis

Ref ID 370 1992

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	77 in total: 20 in group A (counselling), 19 in group B (alarm), 20 in group C (star chart), and 18 in group D (waiting list).
Inclusion/Exclusion Criteria	Inclusion: aged over 5 years, children attending a community mental health clinic with primary NE. Exclusion: organic causes of NE, or mental or developmental problems.
Patient Characteristics	The mean age was 10.05 (sd 2.28) years, the mean baseline wetting over 3 weeks in group A (counselling) was 19.8 (sd 1.73) days, in group B (alarm) was 19.8 (sd 2.14), group C (star chart) was 18.9 (sd 2.21) and in group D (waiting list) was 18 (sd 8.72) days.
Recruitment	Children attending a community mental health clinic with primary NE.
Setting	Israel.
Interventions/ Test/ Factor being investigated	Group A: Cognitive and behavioural self-control education therapy Group B: Pad and bell alarm Group C: star chart - stars were given for a dry night Group D: waiting list
Comparisons	Between treatment groups.
Length of Study/ Follow-up	6 months follow up.
Outcome measures studied	Number of children dry for 3 consecutive weeks, mean number of wet nights in 3 weeks at the end of treatment, failed or relapse after 6 months, and drop out rates.
Results	Stars were given as a reward for a dry night; cognitive behaviour therapy consisted of parents and children being taught 5 components of “modification of misconceptions and irrational beliefs; rational analysis of bedwetting; sensitization to pressure in bladder; self-control training in different situations; exercises in self-observation, charting, and Self assessment and self-reinforcement”. Treatment was for 18 weeks Number of children who were dry for 3 consecutive weeks In group A (counselling) 15 out of 20 children were dry for 3 consecutive weeks compared to 12 out of 19 in group B (alarm), 6 out of 20 in group C (star chart) and 0 out of 18 in group D (waiting list). Mean number of wet nights in 3 weeks at the end of treatment: The mean number of wet nights over 3 weeks at the end of treatment in group A (counselling, 18 children) was 1.03 (sd 2.15). In group B (alarm 15 children) mean was 1.23 (sd 5.28), group C (star chart 14 children) was 3.33 (sd 5.8) and in group D (waiting list 16 children) the mean number of wet nights was 17.22 (sd 9). Number of children who failed or relapsed after 6 months In group A (counselling) 3 out of 18 children failed or relapsed compared to 9 out of 15 in group B (alarm) and 8 out of 14 in group C (star chart).

	Drop out: In group A (counselling) 2 out of 20 children dropped out compared to 4 out of 19 in group B (alarm), 6 out of 20 in group C (star chart) and 11 out of 18 in group D (waiting list).
Safety and adverse effects	None reported.
Does the study answer the question?	The study shows children treated with counselling or alarms were more sucessful than the other treatment groups.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged over 5 years.
Internal Validity	Unclear allocation concealment

van Londen A;van Londen-Barentsen MW;van Son MJ;Mulder GA;

Arousal training for children suffering from nocturnal enuresis: a 2 1/2 year follow-up

Ref ID 338 1993

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	127 in total; no information for each group. At 2.5 years follow up; 113 in total; 38 in group A, 39 in group B and 36 in group C
Inclusion/Exclusion Criteria	Inclusion: aged between 6-12 years
Patient Characteristics	The mean age was 8.6 years, 70% were boys, 87% had primary NE
Recruitment	Not reported
Setting	Netherlands, treatment at home
Interventions/ Test/ Factor being investigated	Group A: alarm with reward stickers for correct behaviour and punishment stickerfor incorrect behaviour Group B: alarm with reward stickers for dry nights and punishment sticker for wet nights Group C: alarm
Comparisons	Between groups A, B and C
Length of Study/ Follow-up	2.5 years
Outcome measures studied	dry for 14 consecutive nights, relapse
Results	20 weeks treatment Dry at 14 nights: In group A (alarm with reward stickers for correct behaviour) 37 out of 38 children achieved 14 dry nights compared to 33 out of 39 in group B (alarm with reward sticker for dry nights and punishment sticker for wet nights) and 26 out of 36 in group C (alarm alone). These differences were significant when comparing group A to group B (binomal test P<0.001) and group C (binomal test P<0.000).

	Relapse at 2.5 years follow up: In group A (alarm with reward stickers for correct behaviour) 10 out of 37 had relapsed at the end of 2.5 year follow up compared to 15 out of 33 in group B (alarm with reward sticker for dry nights and punishment sticker for wet nights) and 13 out of 26 in group C (alarm alone). The two star charts were (1) two reward stickers were given immediately for correct behaviour of waking to the alarm within 3 minutes, going to the toilet after, returning to bed and resetting the alarm, and one sticker was asked for as a charge for incorrect behaviour and (2) two reward stickers were given in the morning for a dry bed or one sticker was asked for as a charge for a wet bed.
Safety and adverse effects	None reported
Does the study answer the question?	The study showed that giving a child an alarm with reward stickers for correct behaviour was significantly more successful in achieving 14 dry nights compared to giving a child an alarm with reward stickers for dry nights and punishment sticker for wet nights or an alarm alone.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Age range is 6-12 years.
Internal Validity	Unclear allocation concealment

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Baker BL;

Symptom treatment and symptom substitution in enuresis

Ref ID 340 1969

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant	30 patients in total
Inclusion/Exclusion Criteria	Patients were excluded if there was an organic cause of wetting
Patient Characteristics	67% were boys. The median age was 8 years with a range of 6-12 years. 4 patients had secondary enuresis. More than half the patients wet every night.
Recruitment	From newpaper adverts
Setting	At home, USA
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: star chart and waking Group C: waiting list
Comparisons	Between treatment groups
Length of Study/ Follow-up	0 months
Outcome measures studied	Change in number of wet nights Self image questionnaire
Results	Star charts were used to keep a record of the child's progress and the child was woken at a set time every night (chosen at start of trial to be before when the child usually wets), once the child was dry for several nights they were not woken for a week, if dry during the week the parents were told if the child wets wake them for the two following nights 10 weeks treatment 10 patients in each group Mean number of wet nights per week in the last 3 weeks of treatment: In group A (alarm) the mean number of wet nights was 1.8, in group B (waking and star chart) the mean number of wet nights was 3.1 and in group C (waiting list) the mean number of wet nights was 5.9. Number of children who achieved 14 consecutive dry nights: In group A (alarm) 11 out of 14 children achieved 14 consecutive dry nights compared to 2 out of 14 in group B (waking and star chart) and 0 out of 14 in group C (waiting list). Relapsed: In total, 4 patients relapsed
Safety and adverse effects	None reported
Does the study answer the question?	Significantly more children became dry for 14 nights when treated with alarm therapy compared to no treatment (79% compared to 0%).
Effect due to factor in study?	Yes.

Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	The age range was 6-12 years.
Internal Validity	Unclear allocation concealment and blinding

Fava GA;Cracco L;Facco L;

Positive reinforcement and enuresis

Ref ID 1751 1981

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	20 in total, 10 in Group A (star chart), 10 in Group B (play therapy).
Inclusion/Exclusion Criteria	Inclusion: primary NE. Wet every night. Exclusion: secondary NE
Patient Characteristics	In Group A (star chart) 6 out of 10 were male, the mean age was 8 (sd 1.66) years There were no baseline characteristics for Group B.
Recruitment	Consecutive children at a child guidance centre.
Setting	Mexico
Interventions/ Test/ Factor being investigated	Group A: behaviour modification – Children were given a star on a chart where the whole family could see and a reward (such as pocket money) for a dry night. If no improvement after 15 nights children were lifted at night to void Group B: unstructured play therapy.
Comparisons	Between treatment groups.
Length of Study/ Follow-up	1 year follow up.
Outcome measures studied	Number of children who achieved 14 consecutive dry nights and number of children who relapsed or failed after 1 year.
Results	The star chart treatment group had a star given by parents on the family calendar, so the whole family could see. For a dry night, a reward for example pocket money was given after each star. Play therapy was described as “unstructured play therapy; behavioural suggestions were carefully excluded”. Treatment was for 3 months Number of children who achieved 14 consecutive dry nights: In Group A (star charts) 8 out of 10 children became dry for 14 consecutive nights (2 of which had to be lifted) compared to 1 out of 10 children in Group B (play therapy). Number of children who relapsed or failed after 1 year In Group A (star charts) 2 out of 10 failed or relapsed compared to 9 out of 10 children in Group B (play therapy).
Safety and adverse effects	None reported
Does the study answer the question?	The study showed that children treated with star charts were more likely to achieve 14 consecutive dry nights compared to children treated with play therapy.
Effect due to factor in study?	Yes

Consistency of results with other studies?	No other studies compared star charts to play therapy.
Directly applicable to guideline population?	Children in treatment group had a mean age of 8 years.
Internal Validity	Unclear allocation concealment and blinding

Maxwell C;Seldrup J;

Factors relating to the optimum effect of imipramine in the treatment of enuresis

Ref ID 540 1971

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	135 in total: cross over trial with 125 in each group due to 10 drop outs.
Inclusion/Exclusion Criteria	Inclusion: aged 5-12 years, normal except for NE, wet at least 3 times a week, stable home environment for 8 weeks. Exclusion: organic causes of NE, MAO inhibitors within previous 2 weeks.
Patient Characteristics	84 out of 125 were male. The age range was 5 to 12 years. Tthe mean baseline number of dry nights in 28 nights was 7 (sd 7).
Recruitment	Not reported.
Setting	UK
Interventions/ Test/ Factor being investigated	Group A: imipramine 25 mg for children aged 5-7 years, 50 mg children aged 8-12 years and star chart. Group B: placebo and star chart.
Comparisons	Between groups A and B
Length of Study/ Follow-up	For 4 weeks consisting of the treatment period.
Outcome measures studied	Mean number of wet nights per month at the end of treatment, adverse events.
Results	Stars (coloured blue) were given for a dry night. After 3 dry nights in a row an extra gold star was given. Treatment was for 4 weeks Mean number of wet nights per month at the end of treatment: In group A (imipramine and star chart) the mean number of wet nights per month was 11.4 (sd 8.7) compared to 14.8 (sd 8.5) nights in group B (placebo and star chart). Adverse events: In group A (imipramine and star chart) 2 out of 125 suffered anorexia, 1 out of 125 suffered diarrhoea, 1 out of 125 suffered constipation, 1 out of 125 suffered depression, 1 had nose bleed, 1 had irritability, 1 had faecal staining, 1 had drowsiness and 1 had oral infection. There were no side effects in group B (placebo and star chart).
Safety and adverse effects	In group A (imipramine and star chart) 2 out of 125 suffered anorexia, 1 out of 125 suffered diarrhoea, 1 out of 125 suffered constipation, 1 out of 125 suffered depression, 1 had nose bleed, 1 had irritability, 1 had faecal staining, 1 had drowsiness and 1 had oral infection. There were no side effects in group B (placebo and star chart).
Does the study answer the question?	The study showed that children treated with imipramine and star chart had fewer wet nights per month compared to those treated with placebo and star chart.

Effect due to factor in study?	Yes
Consistency of results with other studies?	No other studies compared star charts to imipramine.
Directly applicable to guideline population?	Children were aged 5 to 12 years.
Internal Validity	Unclear allocation concealment, well blinded

Question: What is the clinical and cost effectiveness of alarms for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Bradbury MG;Meadow SR;

Combined treatment with enuresis alarm and desmopressin for nocturnal enuresis

Ref ID 372 1995

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant	71 in total: 36 in group A and 35 in group B.
Inclusion/Exclusion Criteria	Inclusion: aged 6-15 years old, and wet at least 1 night per week. Exclusion: if the patient had neuropathetic bladder, urinary tract abnormalities, cystic fibrosis, allergic rhinitis, deafness or learning difficulties, UTI or taking medication which might cause diuresis.
Patient Characteristics	In group A (alarm with desmopressin): 69% were male, the mean age was 10 years old, mean number of dry nights in observation week was 2.3, 39% had family problems, 22% had a Rutter A2 score > 17, 0 had housing problems, 44% had tried enuresis alarms before, 5% also day time wet, and 17% had secondary enuresis. In group B (alarm): 66% were male, the mean age was 9.7 years old, mean number of dry nights in observation week was 2.3, 31% had family problems, 17% had a Rutter A2 score > 17, 0 had housing problems, 37% had tried enuresis alarms before, 6% were also day time wet, and 15% had secondary enuresis.
Recruitment	Referred by GPs, community medical officers, urologists or paediatricians.
Setting	Treatment administered at home, Leeds UK.
Interventions/ Test/ Factor being investigated	Group A: desmopressin with alarm Group B: alarm
Comparisons	Between groups A and B
Length of Study/ Follow-up	6 months.
Outcome measures studied	Change in number of wet nights, numbers of children dry for 4 weeks, and numbers relapsing.
Results	For all children (71) Dry for 4 weeks: In group A (alarm and desmopressin) 27 out of 33 children achieved 4 weeks dry compared to 16 out of 27 in group B (alarm). This difference is significant ($p<0.005$). Relapse: In group A (alarm and desmopressin) 4 children relapsed compared to 3 in group B (alarm). This difference was not significant. Change in mean number of dry nights per week: During the observation period both group A (alarm and desmopressin) and group B (alarm) had a mean number of dry nights of 2.3. At the end of treatment group A (alarm and desmopressin) had a mean number of dry nights of 6.1 compared to 4.8 in group B (alarm). This difference was significant ($P<0.01$) Drop outs In group A (alarm and desmopressin) 0 children dropped out compared to 2 in group B (alarm), this difference was not significant. For children with severe wetting (40) Dry for 4 weeks: In group A (alarm and desmopressin) 14 children achieved 4 weeks dry compared to

6 in group B (alarm), this difference is significant (p<0.01).

Relapse:
In group A (alarm and desmopressin) 2 children relapsed and in group B (alarm) 2 children relapsed.

Change in mean number of dry nights per week:
During the observation period both group A (alarm and desmopressin) had a mean number of dry nights of 0.8 and group B (alarm) had a mean number of dry nights of 1.1.
At the end of treatment group A (alarm and desmopressin) had a mean number of dry nights of 5.7 compared to 3.7 in group B (alarm). This difference was significant (P<0.01)

For children with family and behavioural problems (30)
Dry for 4 weeks:
In group A (alarm and desmopressin) 13 children achieved 4 weeks dry compared to 4 in group B (alarm). This difference is significant (p<0.05).

Relapse:
In group A (alarm and desmopressin) 2 children relapsed and in group B (alarm) 2 children relapsed.

Change in mean number of dry nights per week:
During the observation period both group A (alarm and desmopressin) had a mean number of dry nights of 2.6 and group B (alarm) had a mean number of dry nights of 2.5.
At the end of treatment group A (alarm and desmopressin) had a mean number of dry nights of 6.3 compared to 4.8 in group B (alarm). This difference was significant (P<0.01)

Safety and adverse effects

None reported

Does the study answer the question?

In all patients significantly more children became dry for 4 weeks in alarm and desmopressin than the alarm alone group. Children who had alarm with desmopressin had significantly more dry nights than those who had alarm therapy alone. There was no significant difference between the relapse rate and drop out rate.
In children with behavioural and family problems significantly more children became dry for 4 weeks in alarm and desmopressin than the alarm alone group. Children who had alarm with desmopressin had significantly more dry nights than those who had alarm therapy alone. There was no difference between the relapse rate.
No difference in relapse
In severe wetting group significantly more children became dry for 4 weeks in alarm and desmopressin than the alarm alone group. Children who had alarm with desmopressin had significantly more dry nights than those who had alarm therapy alone. There was no difference between the relapse rate.

Effect due to factor in study?

Yes.

Consistency of results with other studies?

No other studies considered this subgroup.

Directly applicable to guideline population?

Children were aged 6 - 15 years old.

Internal Validity

Butler RJ;Forsythe WI;Robertson J;

The body-worn alarm in the treatment of childhood enuresis

Ref ID 362 1990

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	In study 1: 40 in total, 20 in each group In study 2: 48 in total, 24 in each group
Inclusion/Exclusion Criteria	Study 1 Inclusion: wet at least 4 nights a week for a month, normal physical examination, normal urine microscopy, normal intelligence, not previously treated for NE with any conditioning method.
Patient Characteristics	Study 1 The mean age was 8.11 years (range 6.1-15.6 years). 63% were boys. In group A the mean age was 8.2 years, the baseline number of dry nights was 1.2 and the male to female ratio was 14:6. In group B the mean age was 9.1 years, the baseline number of dry nights was 0.7 and the male to female ratio was 11:9.
Recruitment	Referred as out-patients for treatment of NE.
Setting	Leeds, UK, treatment administered at home.
Interventions/ Test/ Factor being investigated	Study 1 Group A: pad and bell alarm Group B: body worn alarm
Comparisons	Between group A and B in each study
Length of Study/ Follow-up	6 months
Outcome measures studied	Number of children dry for 14 consecutive nights, change in number of wet nights, and relapses.
Results	16 weeks treatment. Success was reaching 14 consecutive dry nights. Study 1: Both alarms were 70% effective: 14 out of 20 children became dry for 14 consecutive nights. The drop out rate was 15%: 3 out of 20 children for the pad and bell alarm and 10% 2 out of 20 children for the body-worn alarm. There were no statistical differences between groups. The relapse rates at 6 months were 4 out of 14 children for the pad and bell alarm and 3 out of 14 children for the body-worn alarm. There was no statistical difference between groups. The mean number of wet nights per week at end of treatment for the pad and bell alarm was 1.2 compared to 1 for the body worn alarm. Study 2: 16 weeks treatment 14 consecutive dry nights: In group A (DBT) 14 out of 24 children achieved 14 consecutive dry nights compared to 20 out of 24 in group B (alarm). The difference was not statistically significant. The mean number of wet nights before achieving 14 consecutive dry nights was 53.7 in group A (DBT) and 40.7 in group B (alarm). There was an immediate response with both interventions, and from week 3 the body-worn alarm group consistently achieved more dry nights. The difference was significant at week 3 ($t=2.28$, $df=43$, $p<0.05$); and week 4 ($t=2.26$, $df=42$, $p<0.05$). At week 7 the children in the MDBT group achieved the same number of dry nights as the body-worn alarm group did in week 3. Mean number of wet nights in 16 weeks In group A (DBT) the mean number of wet nights was 28.7 compared to 25 in group B (alarm). The difference was not statistically significant. The mean number of wet nights per week at end of treatment for the alarm was 1.6 compared to 1.8 for the MDBT. Number of children who relapsed: 7 out of 14 of the DBT group relapsed within 6 months, and 9 out of 20 relapsed in the alarm group. Number of drop outs: 1 out of 24 children dropped out of the alarm group compared to 2 out of 24 in the DBT group.

Safety and adverse effects	None reported
Does the study answer the question?	It compares two types of alarms, the body-worn alarm and the pad and bell (modified dry-bed training). Both were equally effective in the first study (70%) and the second study initial arrest was 58% for the MDBT group and 83% for the body-worn alarm group, however the difference was not significant. The body-worn alarm achieved a greater number of dry nights earlier than the other group. The relapse rate was higher in the second study than the first study, the difference between groups was not significant.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged between 6.1 years and 15.6 years.

Internal Validity

Leebeek-Groenewegen A;Blom J;Sukhai R;Van D;

Efficacy of desmopressin combined with alarm therapy for monosymptomatic nocturnal enuresis

Ref ID 258 2001

Study Type	Randomised Controlled Trial	**Funding**	Ferring B. V., Hoofddorp, the Netherlands

Number of participant	93 in total: 47 in group A and 46 in group B.
Inclusion/Exclusion Criteria	Inclusion: uncomplicated NE, and wet for at least 3 nights per week. Exclusion: treatment in previous 2 weeks for NE, day time wetting, pollakisuria, use of medication which interacts with desmopressin, underlying cardiovascular, hepatic, urological, or psychiatric disease, or insufficient motivation for use of alarm.
Patient Characteristics	The age range was 6-14 years old. No other characteristics given.
Recruitment	Patients seen in 2 specialist enuresis clinics as part of a Dutch general paediatric outpatient department.
Setting	Treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm with desmopressin for 3 weeks, then desmopressin for 3 weeks and then alarm for 3 weeks. Group B: alarm and placebo for 6 weeks then alarm for 3 weeks.
Comparisons	Between group A and B.
Length of Study/ Follow-up	6 months.
Outcome measures studied	The number of children who had a greater than 90% reduction in mean number of wet nights, mean number of wet nights, and the number of children who had a greater than 90% reduction in mean number of wet nights at 6 months.
Results	The number of children who had a greater than 90% reduction in mean number of wet nights: In the alarm and desmopressin group 15 out of 43 children achieved a 90% reduction compared to 18 out of 38 in the alarm and placebo group. Mean number of wet nights: The mean number of wet nights in the alarm and desmopressin group was 2.77 compared to 2.21 in the alarm and placebo group.

	The number of children who had a greater than 90% reduction in mean number of wet nights at 6 months: In the alarm and desmopressin group 17 out of 41 children achieved a 90% reduction at 6 months compared to 17 out of 37 in the alarm and placebo group.
Safety and adverse effects	None.
Does the study answer the question?	The authors stated that alarm with desmopressin resulted in significantly fewer wet nights during first 3 weeks compared to alarm alone but there was no significant difference at 6 months. There was no difference in the number of children cured at 2 weeks after treatment or at the 6 month follow up.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged between 6 -14 years old.
Internal Validity	Unclear allocation concealment

Longstaffe S;Moffatt ME;Whalen JC;

Behavioral and self-concept changes after six months of enuresis treatment: a randomized, controlled trial

Ref ID 71 2000

Study Type	Randomised Controlled Trial	**Funding**	National Health Research and Development Program and Fering Inc

Number of participant	182 in total, 61 in group A, 60 in group B
Inclusion/Exclusion Criteria	Inclusion: aged over 7 years, monosyptomatic NE, wetting at least 12 times in a 4 week period, normal urinalysis, no history of fecal soiling and signs of normal bladder functioning. Exclusion: neurological or developmental abnormalities, diabetes insipidus, diabetes mellitus, chronic renal disease, history of constipation, or already having desmopressin or alarm therapy.
Patient Characteristics	In group A (alarm): 78.7% were male, 37.7 % were first born, 13.4% had a past history of UTI, 24.6% had a history of constipation. 94.9% had tried fluid restriction, 90% had tried lifting, 53.3% had tried behavioural techniques, 3.4% had tried bladder exercises, 20% had tried alarms, 13.3% had tried desmopressin, 14.3% had tried imipramine, and 10.9% had tried oxybutnin. 36.2% had family history of NE on both sides, 41.4% had family history of NE on one side. In group B (intranasal desmopressin): 75% were male, 41.7% were first born, 6.7% had a past history of UTI, 23.3% had a history of constipation. 90% had tried fluid restriction, 86.7% had tried lifting, 58.3% had tried behavioural techniques, 11.7% had tried bladder exercises, 18.3% had tried alarms, 21.7% had tried desmopressin, 16.7% had tried imipramine, and 8.6% had tried oxybutnin. 41.7% had family history of NE on both sides, 41.7% had family history of NE on one side.
Recruitment	Phycisian adverts, newspaper adverts, posters and radio.
Setting	Treatment administered at home, Canada.
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: intranasal desmopressin
Comparisons	Between treatment groups.

Length of Study/ Follow-up	6 months.
Outcome measures studied	Number of children achieveing 14 dry nights, and self concept changes.
Results	6 months treatment 14 consecutive dry nights: In group A (alarm) 35 children out of 61 (57%) achieved 14 dry nights compared to 29 out of 60 children (48%) in group B (desmopressin). Drop out: 17 children in total dropped out. 8 were from group A (alarm) and 5 from group B (desmopressin). Behavioural changes: The behavioural changes were not related to the type of treatment or success of treatment. However there were significant positive changes in intellectual, physical appearance, anxiety, popularity (analysed through the Piers-Harris Subscales). There were also significant positive results on the Achenbach CBCL, Internalizing and Externalizing Behaviour Scores and Social, Thought and Attention Problems Subscales.
Safety and adverse effects	None reported.
Does the study answer the question?	There was no significant difference in the number of children achieving 14 consecutive dry nights between those receiving alarm and those receiving desmopressin. The study also reported a positive change in the children's behaviour; however this was not related to treatment type or outcome success.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar with other studies comparing alarms to desmopressin.
Directly applicable to guideline population?	Children were aged over 7 years.
Internal Validity	Unclear blinding

Lynch NT;Grunert BK;Vasudevan SV;Severson RA;

Enuresis: comparison of two treatments

Ref ID 137 1984

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	60 children; 20 in control group, 20 in classic conditioning treatment, 20 in the bell and pad apparatus.
Inclusion/Exclusion Criteria	Inclusion: wet at least 2 times a week. Exclusion: day time wetting.
Patient Characteristics	The age range was 5-12 years.
Recruitment	Selected from a pool of children in the first 3 grades at the local school and from paedatric referrals.
Setting	At home.

Interventions/ Test/ Factor being investigated	Group A: star chart for 2 weeks and then an alarm Group B: control - no treatment, waiting list group
Comparisons	Between groups A and B.
Length of Study/ Follow-up	10 weeks.
Outcome measures studied	Number of children dry for 14 consecutive dry nights, change in number of wet nights, and drop out rates.
Results	10 weeks treatment 14 consecutive nights dry: In group A (star chart then alarm) 7 out of 18 children (39%) became dry for 14 nights compared to 0 out of 18 (0%) in group B (control) Change in number of wet nights: At baseline group A (star chart then alarm) had a mean number of wet nights of 11.11 (SD 2.90), and group B (control) had a mean number of 11.55. During the last week of treatment group A (star chart then alarm) had a mean number of wet nights of 1.69 (SD 2.28) and group B (control) 5.15 (SD 1.5). Drop outs 1 child dropped out from the alarm group compared to none in the waiting list group. The study reported that the alarms did malfunction during the treatment which may have affected the results.
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that giving the child an alarm was more effective than no treatment.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies comparing alarms to no treatment.
Directly applicable to guideline population?	Children's age range was 5-12 years.
Internal Validity	Unclear bllinding

Nawaz S;Griffiths P;Tappin D;

Parent-administered modified dry-bed training for childhood nocturnal enuresis: Evidence for superiority over urine-alarm conditioning when delivery factors are controlled

Ref ID 54 2002

Study Type	Randomised Controlled Trial	**Funding**	None reported

Number of participant	36 in total, 12 in each of the three study groups.
Inclusion/Exclusion Criteria	Inclusion: functional NE defined in DSM-IV (aged over 5 years, wet at least 2 times a week for 3 months, NE not due to primary medical or physiological pathology), aged between 7-12 years, attending a mainstream school, wetting 4 or more nights a week, no forseen domestic disruption during treatment time, readiness to be involved in trial, bedwetting secondary to organic or psychiatric disorder and those unwilling to cooperate. Exclusion: diurnal enuresis or encopresis.

Patient Characteristics	In group A, Dry-bed training (DBT) with alarm, the mean age was 9.93 years (1.81 SD), 50% were male, the mean baseline number of wet nights per week was 5.58 (1.31 SD), The mean deprivation category (0-7) was 4.67 (2.15 SD) In group B (alarm) the mean age was 9.93 years (1.99 SD), 50% were male, the mean baseline number of wet nights per week was 5.50 (1.45 SD), The mean deprivation category (0-7) was 4.75 (1.91 SD) In group C (control-no treatment) the mean age was 9.84 years (1.84 SD), 50% were male, the mean baseline number of wet nights per week was 5.92 (1.08 SD), The mean deprivation category (0-7) was 5.75 (1.71 SD)
Recruitment	From nine health centres (GPs, GP nurses, health visitors, community paediatricians)
Setting	Scotland, UK, treatment at home.
Interventions/ Test/ Factor being investigated	Group A: DBT with alarm Group B: alarm Group C: control group - no treatment
Comparisons	Between groups A, B and C
Length of Study/ Follow-up	6 months
Outcome measures studied	Dry for 14 consecutive nights, change in number of wet nights, and relapse.
Results	Patients were treated for 16 weeks or until dry Dry for 14 consecutive nights: In group A (DBT with alarm) 8 out of 12 children (67%) became dry for 14 nights compared to 3 out of 12 children (25%) in group B (alarm) and 1 out of 12 children (8%) in group C (control). This difference was significant ($p<0.01$) Change in number of wet nights: The mean number of wet nights for group A (DBT and alarm) was 0.83 (sd 1.4) compared to 3.25 (sd 2.67) for group B (alarm) and 5 (sd 2.26) for group C (control) Relapse: At 3 month follow up, no children had relapsed. At 6 month follow up 1 child in group A (DBT with alarm) and 1 child in group B (alarm) had relapsed). Both children were wetting 3 nights a week.
Safety and adverse effects	None reported
Does the study answer the question?	The study showed that DBT with alarm was significantly more effective at achieving 14 dry nights compared to alarm alone and no treatment. The study also showed that DBT with alarm had a greater reduction in the mean number of wet nights compared to alarm alone and no treatment.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other studies for this sub group.
Directly applicable to guideline population?	The age range was 7-12 years.
Internal Validity	Unclear allocation concealment

Ng CFN;Wong SN;Hong Kong Childhood Enuresis Study Group.;

Comparing alarms, desmopressin, and combined treatment in Chinese enuretic children

Ref ID 369 2005

Study Type	Randomised Controlled Trial	**Funding**	Hong Kong Paediatric Nephrology Society with a research grant from Ferring Pharmaceuticals Limited

Number of participant	105 in total: 35 in group A, 38 in group B, 32 in group C.
Inclusion/Exclusion Criteria	Inclusion: Primary NE, age range 7-15 years, wetting at least 3 times a week in baseline 2 weeks. Exclusion: UTI in previous 3 months, day time wetting, polyuric disorders, abnormal urinanalysis, renal disease, previous diuretics, unwilling to be randomised previous treatment of alarms, desmopressin or tricyclics
Patient Characteristics	The mean age was 9.5 (1.8 SD) years,and the age range 7-12 years. In group A (alarm) the mean age was 9.5 (1.8 SD) years, 57% children were in the age range 7-9 years, 40% in 10-12 years and 3% in 13-15 years. 63% were boys, and the mean baseline number of wet nights a week was 5.1 (1.5 SD). In group B (desmopressin) the mean age was 9.2 (1.8 SD) years, 69% children were in the age range 7-9 years, 26% in 10-12 years and 5% in 13-15 years. 68% were boys, and the mean baseline number of wet nights a week was 5.3 (1.4 SD). In group C (alarm with desmopressin) the mean age was 9.8 (1.2 SD) years, 50% children were in the age range 7-9 years, 47% in 10-12 years and 3% in 13-15 years. 66% were boys, and the mean baseline number of wet nights a week was 4.9 (1.2 SD).
Recruitment	Patients presented to 9 public hospitals in Hong Kong with primary NE.
Setting	Hong Kong, and treatment administered at home.
Interventions/ Test/ Factor being investigated	Gourp A: alarm Group B: oral desmopressin Group C: alarm with oral desmopressin
Comparisons	Between groups A, B and C.
Length of Study/ Follow-up	12 weeks.
Outcome measures studied	Number of children who were dry for 14 consecutive nights, change in number of wet nights, drop out, and relapse.
Results	12 weeks treatment Dry for 14 consecutive nights: In group A (alarm) 8 out of 35 children achieved 14 dry nights, compared to 16 out of 38 children, in group B (desmopressin) and 20 out of 32 children in group C (alarm and desmopressin). This difference was significant p = 0.014. The mean number of wet nights per week at end of treatment for the alarm group was 2.8 (SD 2.2) compared to 2.7 (SD 2.4) for the desmopressin group and 1.3 (SD 1.9) for the desmopressin and alarm group. Drop out: 12 children dropped out in total, 7 out of 35 (20%) from group A (alarm), 2 out of 38 (5%) from group B (desmopressin) and 3 out of 32 (9%) from group C (alarm and desmopressin). Relapse: In the alarm group 0 out of 8 children relapsed at 3 months, compared to 9 out of 16 in the desmopressin group and 7 out of 20 in the alarm with desmopressin group.
Safety and adverse effects	None.

Does the study answer the question?	The study showed that significantly more patients achieved 14 consecutive dry nights if they were treated with alarm or desmopressin alone (71% compared to 42.9% and 52.6%. The study also showed that there was a significant difference between groups in the % reduction of wet nights during the last 4 weeks of treatment and during the first 4 weeks of follow up, with patients being treated with alarm and desmopressin being significantly more successful than alarm or desmopressin alone.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies with same comparison.
Directly applicable to guideline population?	Age range was 7-15 years.
Internal Validity	Unclear blinding

Sukhai RN;Mol J;Harris AS;

Combined therapy of enuresis alarm and desmopressin in the treatment of nocturnal enuresis

Ref ID 353 1989

Study Type	Randomised Controlled Trial	**Funding**	Ferring B.V, Holland provided Minrin Nasal pipettes

Number of participant	28 in total: 28 in each group. Patients switched groups after 2 weeks.
Inclusion/Exclusion Criteria	Inclusion: normal urine concentration capacity of 800 mosmol/kg or higher, wet 3 or more nights a week, no neurological or renal disorder, no history of daytime wetting, no chronic urinary tract infection, and no neurological or cardiovascular disease.
Patient Characteristics	The mean age was 11 (2.4 SD) years, 75% were boys, 71% attended normal primary school and 29% attended classes or schools for those with learning difficulties. 31% had a positive family history of bed wetting and 65% had previously tried treatment for NE. The mean number of dry nights per week before starting treatment was 1.4 (0.3 SD).
Recruitment	Not reported.
Setting	Holland, treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm with desmopressin. Group B: alarm with placebo.
Comparisons	Between groups A and B.
Length of Study/ Follow-up	6 months follow up.
Outcome measures studied	The mean number of dry nights per week.
Results	2 weeks of each treatment with 2 week washout. The mean number of dry nights per week: In the alarm and desmopressin the mean number of dry nights per week was 5.1 (sd 0.4) compared to 4.1 (sd 0.4) in the alarm and placebo group.
Safety and adverse effects	None reported.
Does the study answer the question?	Alarm and desmopressin had a greater number of dry nights after treatment compared to alarm and placebo.

Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Age range was 7-16 years.
Internal Validity	Unclear allocation concealment

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Baker BL;

Symptom treatment and symptom substitution in enuresis

Ref ID 340 1969

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant	30 patients in total: 14 in each of the two groups.
Inclusion/Exclusion Criteria	Patients were excluded if there was an organic cause of wetting.
Patient Characteristics	67% were boys. The median age was 8 years with a range of 6-12 years. 4 patients had secondary enuresis. More than half the patients wet every night.
Recruitment	From newpaper adverts.
Setting	At home, USA
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: control group - not treatment (waiting list) The study also considered regular waking which was not included as it is not a relevant comparator
Comparisons	Between groups A and B
Length of Study/ Follow-up	10 weeks.
Outcome measures studied	Mean number of wet nights, numbers of children who were dry for 14 consecutive nights, and relapse.
Results	10 weeks treatment Dry for 14 consecutive nights: In group A (alarm) 11 out of 14 children became dry for 14 nights compared to 0 out of 14 children in group B (control). Mean number of wet nights: In group A (alarm) the mean number of wet nights per 3 weeks was 1.8 compared to 5.9 in group B (control). Relapsed: In total, 4 patients relapsed
Safety and adverse effects	None reported
Does the study answer the question?	Significantly more children became dry for 14 nights when treated with alarm therapy compared to no treatment (79% compared to 0%).
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies with same comparison.
Directly applicable to guideline population?	The age range was 6-12 years.
Internal Validity	Unclear allocation concealment and blinding

Bennett GA;Walkden VJ;Curtis RH;Burns LE;Rees.J.;Gosling JA;

Pad-and-buzzer training, dry-bed training, and stop-start training in the treatment of primary nocturnal enuresis

Ref ID 360 1985

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant	40 in total: 9 in group A (pub and buzzer training), 12 in group B (stop start training), 10 in group C (dry bed training), 9 in group D (control-waiting list)
Inclusion/Exclusion Criteria	Inclusion: primary NE, not dry for more than 4 weeks, at least 6 wet nights during 14 night baseline, negligible daytime wetting. Exclusion: encopresis, previous behavioural intervention, or gross psychopathology.
Patient Characteristics	63% were boys. The mean age was 8.5 (3.2 SD) years and the age range was 5-12 years.
Recruitment	Referred from GP.
Setting	Treatment administered at home, Rochdale UK.
Interventions/ Test/ Factor being investigated	Group A: alarm (pad and buzzer) Group B: dry bed training (DBT) with alarm The study also considered star charts, bladder training and sphincter muscle exercises which was not included as it is not a relevant comparator.
Comparisons	Between treatment groups.
Length of Study/ Follow-up	12 weeks
Outcome measures studied	Number of children achieving 14 consecutive dry nights, mean number of dry nights at follow up,and drop outs.
Results	12 weeks treatment Results: Dry for 14 consecutive nights: In group A (alarm) 4 out of 9 children, became dry for 14 nights compared to 5 out of 10 children, in group B (DBT with alarm). Drop out: 32 children in total dropped out In group A (alarm) 9 children, dropped out compared to 10 children in group B (DBT with alarm) Mean number of wet nights: The mean number of wet nights per week at end of treatment for the alarm group was 1 (SD 1.95) compared to 1.4 (SD 1.8) for the dry bed training group and 5.15 (SD 1.5) for the no treatment alarm group.
Safety and adverse effects	None reported
Does the study answer the question?	Both alarm alone and DBT with alarm gave good results for achieving 14 dry nights (44% and 50%). All patients in the treatment groups saw an increase in the number of dry nights over the 12 week follow up, with alarms having the highest number of wet nights then DBT with alarm. There was no significant difference in the number of drop outs in each group.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies with same comparison.

Directly applicable to guideline population?	Yes the age range was 5-12 years old.
Internal Validity	Unclear allocation concealment and blinding

Bollard J;Nettelbeck T;

A comparison of dry-bed training and standard urine-alarm conditioning treatment of childhood bedwetting

Ref ID 371 1981

Study Type	Randomised Controlled Trial	**Funding**	Research undertaken as part requirement for the degree of doctor of philosophy.

Number of participant	120 children: 20 in each of the 6 groups.
Inclusion/Exclusion Criteria	Inclusion: through medical examination, wet at least 1 night a week, and no other treatment during study. Exclusion: organic causes of NE.
Patient Characteristics	In group A (DBT with therapist in home) children had a mean age of 9.3 years and 14 were male. The baseline mean number of wet nights was 5.8. In group B (DBT with therapist in hospital) children had a mean age of 8.11 years and 13 were male. The baseline mean number of wet nights was 5.2. In group C (DBT with parents as therapist in home) children had a mean age of 9.7 years and 16 were male. The baseline mean number of wet nights was 6.0. In group D (DBT with parents as therapist in home without alarm) children had a mean age of 8.6 years and 14 were male. The baseline mean number of wet nights was 5.7. In group E (alarm) children had a mean age of 8.8 years and 14 were male. The baseline mean number of wet nights was 6.0. In group F (waiting list) children had a mean age of 8.1 years and 1 were male. The baseline mean number of wet nights was 4.7.
Recruitment	Children who were outpatients of the Adelaide Children's Hospital.
Setting	Outpatient service of Adelaide Children's Hospital
Interventions/ Test/ Factor being investigated	Group A: DBT with therapist in home Group B: DBT with therapist in hospital Group C: DBT with parents as therapist in home Group D: DBT with parents as therapist in home without alarm Group E: Alarm Group F: Waiting list
Comparisons	Between treatment groups.
Length of Study/ Follow-up	Follow up at 3, 6 and 12 months.
Outcome measures studied	Number of children achieving 14 consecutive dry nights, mean number of wet nights per week at the end of week 20, and numbers relapsing.
Results	Dry bed training included: waking schedule, retention control training, positive practice and cleanliness training Treatment was until patient achieved 14 consecutive dry nights or for 20 weeks 14 consecutive dry nights: In group A (DBT with therapist in home) 20 out of 20 achieved 14 consecutive dry nights compared to 20 out of 20 in group B (DBT with therapist in hospital), 20 out of 20 in group C (DBT with parents as therapist in home), 5 out of 20 in group D (DBT with parents as therapist in home without alarm), 16 out of 20 in group E (alarm) and 2 out of 20 in group F (waiting list). Mean number of wet nights per week at the end of week 20: In group A (DBT with therapist in home) the mean number of wet nights was 0

compared to 0 in group B (DBT with therapist in hospital), 0 in group C (DBT with parents as therapist in home), 3.8 in group D (DBT with parents as therapist in home without alarm), 0.6 in group E (alarm) and 4.4 in group F (waiting list).

Number of children who relapsed:
In group A (DBT with therapist in home) 5 out of 20 relapsed compared to 6 out of 20 in group B (DBT with therapist in hospital), 4 out of 20 in group C (DBT with parents as therapist in home), 2 out of 5 in group D (DBT with parents as therapist in home without alarm), 6 out of 16 in group E (alarm) and 2 out of 2 in group F (waiting list).

Safety and adverse effects None reported.

Does the study answer the question? Study showed children treated with DBT and an alarm were more likely to achieve 14 consecutive dry nights and have fewer wet nights compared to children treated with DBT and no alarm, alarm or no treatment.

Effect due to factor in study? Yes.

Consistency of results with other studies? Similar to results from other studies comparing DBT with an alarm to an alarm and control groups.

Directly applicable to guideline population? Mean ages of children in each group ranged from 8.1 to 9.7.

Internal Validity No blinding, unclear allocation concealment.

Bollard J;Nettelbeck T;

A component analysis of dry-bed training for treatment for bedwetting

Ref ID 342 1982

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant N=127 children; 35 in standard conditioning group, 12 in waking schedule, 12 in retention control training, 12 in positive practice and clanliness training, 12 in waking and retention control training, 12 in waking, positive practice and cleanliness training, 12 in retention control training, positive practice and cleanliness traing, 20 in dry bed training.

Inclusion/Exclusion Criteria Organic causes of nocturnal enuresis excluded
Daytime wetting exclusion not mentioned.

Patient Characteristics Children with thorough medical examination; regularly wetting at least one night per week; no other treatment during trial. Previous treatment: no details.

Mean age
A: 9.3
B: 8.11
C: 9.7
D: 8.6

Recruitment Not reported

Setting Australia, treatment at home

Interventions/ Test/ Factor being investigated Experiment 2

Group A (20): DBT (A+W+CT+PP) with therapist at home
Group B (20): DBT (A+W+CT+PP) with therapist at hospital
Group C (20): DBT (A+W+CT+PP) with parents as therapists at home
Group D (20): DBT (W+CT+PP) with parents as therapists at home without enuresis alarm
Group E: alarm
Group F: waiting list control

Comparisons	Between treatment groups
Length of Study/ Follow-up	Duration of treatment: until 14 consecutive dry nights or 20 weeks. Follow-up at 3, 6 and 12 months
Outcome measures studied	14 consecutive dry nights, mean number of wet nights
Results	DBT compared to alarm only. DBT significantly more effective in terms of number of wet nights and days to dryness compared to alarm. Mean number of wet nights per week at the end of week 20. (including drop-outs) A:0; B:0; C:0; D: (n=20) 3.8; E: 0.6; F:4.4 (excluding drop-outs) A:0; B:0; C:0; D: (n=8) 1.3; E:0.6; F:4.4 Number achieving 14 consecutive dry nights: A:20; B:20; C:20; D:5; E:16; F:2. $p<0.05$.
Safety and adverse effects	None reported
Does the study answer the question?	DBT compared to alarm only. DBT significantly more effective in terms of number of wet nights and days to dryness.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to results in Bolard 1981
Directly applicable to guideline population?	Mean age range of 8.6 to 9.7 years
Internal Validity	Unclear allocation concealment and blinding.

Danquah SA;

Comparative treatment of nocturnal enuresis among Ghanaian school children

Ref ID 364 1975

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant	30 boys, 10 in each treatment group (three goups)
Inclusion/Exclusion Criteria	Inclusion: boys with enuresis Exclusion: those who were undergoing tradional treatment
Patient Characteristics	The mean age was 10.4 years, the mean IQ is 85.4 (20.12 SD)
Recruitment	From a fishing village in Ghana
Setting	Ghanian fishing community, at home
Interventions/ Test/ Factor being investigated	Group A: amitripyline Group B: alarm The study also looked at shaming which is not a relevent comparison so results are not reported
Comparisons	Between treatment groups.
Length of Study/ Follow-up	3 months
Outcome measures studied	Change in number of wet nights

Results	7 weeks treatment The mean number of wet nights per week at the end of treatment was 3.2 for the alarm group and 4 for the amitripyline group. The median number of days for initial arrest were 15.5 for alarm therapy and 20 for amitriptyline Follow-up was conducted after 3 months after treatment. Alarm therapy was the only treatment that was continuously successful. The post-treatment ranking was 3.20 and following treatment was 1.49, t=3.98, p<0.001.
Safety and adverse effects	None reported
Does the study answer the question?	The alarm was found to be quicker and more effective than amitriptyline.
Effect due to factor in study?	Yes (NB there is a spontaneous 15% cure rate)
Consistency of results with other studies?	
Directly applicable to guideline population?	The study only included boys, the mean age was 10.4 years
Internal Validity	Unclear allocation concealment and blinding

Fielding D;

The response of day and night wetting children and children who wet only at night to retention control training and the enuresis alarm

Ref ID 146 1980

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	45 patients who only night time wet, and 30 patients who night and day time wet.
Inclusion/Exclusion Criteria	Patients had to wet the bed at least once a week. They had to be aged between 5 and 15 years, have no UTI, no evidence of organic cause of NE and have not been treated in the previous 12 months. Children who day time wet only were excluded.
Patient Characteristics	Of the night time wetters: 30 patients were male, the age ranged from 5 years and 2 months to 13 years and 10 months. The mean age of males was 9.08 ± 4.54 years and in females was 7.96 ± 5.53 years. Of day time and night time wetters: 24 were female. The age ranged from 5 years to 12 years and 5 months. The mean age of males was 7.96 ± 2.40 years and in females was 7.08 ± 2.83 years.
Recruitment	Patients were referred by paediatricians and psychiatrists to 2 clinics set up for the study.
Setting	Treatment administered at home, Liverpool, UK.
Interventions/ Test/ Factor being investigated	Group A: retention control and alarm Group B: alarm only
Comparisons	Between study groups and between night and day wetters and night time only wetters.
Length of Study/ Follow-up	12 months

Outcome measures studied	Number of children achieving 14 consecutive dry nights, drop out rates and relapse rates.
Results	14 weeks treatment The patients were treated for 4 weeks of retention control training and 14 weeks with the alarm. The results are reported in two subgroups, patients who have only night time wetting and those who have both night and day time wetting. After one month all children received the alarm only intervention. For patients with night time only wetting: 14 consecutive dry nights: In group A (retention control with alarm) 11 out of 16 children (69%) became dry for 14 nights compared to 14 out of 17 children (82%) in group B (alarm). Drop out: 24.4% dropped out in total (11 out of 45 children) Relapse: At 6 month follow up 5 out of 14 (35.7%) had relapsed in the alarm group compared to 3 out of 11 (27.7%) in the alarm and RCT group. At 12 month follow up 8 out of 14 (57.1%) had relapsed in the alarm group compared to 4 out of 11 (36.4%) in the alarm and RCT group. These differences are not significant. For patients with night and day time wetting: 14 consecutive dry nights: In group A (retention control with alarm) 6 out of 8 children (75%) became dry for 14 nights compared to 3 out of 8 children (38%) in group B (alarm). Drop out: 40% dropped out in total (12 out of 30 children) Relapse: At 6 month follow up 2 out of 3 children (66.7%) had relapsed in the alarm group compared to 4 out of 6 children (66.7%) in the alarm and RCT group. At 12 month follow up 2 out of 3 children (66.7%) had relapsed in the alarm group compared to 4 out of 6 children (66.7%) in the alarm and RCT group. There is no difference in the two treatment groups. However children with day and night time wetting relapsed earlier than those who just night time wet.
Safety and adverse effects	None reported.
Does the study answer the question?	The study shows that for children who wet only at night time, alarms are more effective at achieving 14 consecutive dry nights. However for children who night and day time wet, retention control and alarm treatment is more effective. There was not significant differences between treatment groups in the number of relapses, but children who night and day time wet relapsed earlier than those who only night time wet.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Population was correct (boys and girls aged between 5 and 15 years old).
Internal Validity	Unclear allocation concealment and blinding

Fournier JP;Garfinkel BD;Bond A;Beauchesne H;Shapiro SK;

Pharmacological and behavioral management of enuresis

Ref ID 346 1987

Study Type	Randomised Controlled Trial	**Funding**	Not reported

Number of participant	64 in total, 8 in each group
Inclusion/Exclusion Criteria	Inclusion: aged between 5 and 14 years, no history of UTI or disease, no physical or neurological disorder, at least 2 wet nights a week for previous 6 months, no treatment in previous 3 months, no significant cognitive impairment or mental retardation, imformed consent to random allocation of treatment
Patient Characteristics	73% were boys, the mean age was 8.5 years, 70% of children lived with their biological parent, 14% lived with a single parent, 83% were either the oldest or second eldest child in their family, 77% had had a first degree relative with enuresis and 61% had another relative with enuresis
Recruitment	Newspaper adverts and referred from paediatricians.
Setting	Treatment administered at home, Montreal Canada.
Interventions/ Test/ Factor being investigated	Group A: imipramine Group B: alarm Group C: alarm with imipramine The study also considered placebo and random waking, these have not been included as not relevant comparators.
Comparisons	Between treatment groups.
Length of Study/ Follow-up	3 months.
Outcome measures studied	Change in number of wet nights, and drop outs.
Results	6 weeks treatment In the alarm group 1 out of 8 children dropped out compared to 1 out of 8 in the imipramine group and 0 out of 8 in the alarm and imipramine group. In the alarm group the mean number of wet nights during the last week of treatment was 2.5 compared to 1.9 in the imipramine group and 1 in the alarm and imipramine group. Drop out: In total 4 boys dropped out due to side-effects or non-compliance and 1 girl dropped out due to having a UTI.
Safety and adverse effects	None reported
Does the study answer the question?	The study showed that imipramine had a faster effect than the other treatments. However at 4 weeks the most effective treatments were alarm, alarm with imipramine and imipramine alone. At the 3 month follow up the most sucessful treatments were alarm and imipramine.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged 5 - 14 years old.
Internal Validity	Unclear allocation concealment and blinding

Geffken G;Johnson SB;Walker D;

Behavioral interventions for childhood nocturnal enuresis: the differential effect of bladder capacity on treatment progress and outcome

Ref ID 121 1986

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	50 in total: 10 patients dropped out which left 10 in each of the four groups
Inclusion/Exclusion Criteria	Inclusion: aged 5-13 years, NE for at least 3 months, and wetting at least 2 times a week.
Patient Characteristics	66% were boys. There was no significant difference between the groups in terms of age or sex.
Recruitment	Referral from departments of paedatrics from Univeristy of Florida and Univeristy of Virgina.
Setting	Florida and Virgina, USA, at home
Interventions/ Test/ Factor being investigated	Group A: alarm (large maximal functional bladder capacity) Group B: alarm (small maximal functional bladder capacity) Group C: alarm with retention control (large maximal functional bladder capacity) Group D: alarm with retention control (small maximal functional bladder capacity)
Comparisons	Between group A and C and between group B and D.
Length of Study/ Follow-up	8 weeks or more.
Outcome measures studied	Number of children dry for 14 consecutive nights, change in number of wet nights, and relapse.
Results	14 weeks treatment Over all 92.5% (37 out of the 40) patients were dry for 14 consecutive nights; 2 of the patients who did not become dry during treatment became dry during followup. 41% (16 out of 39) patients relapsed during an 8 week follow up (relapse was wet 3 or more nights during a 2 week period). The patients were divided into two groups those with a large maximal functional bladder capacity and those with a small maximal bladder capacity. Dry for 14 consecutive nights: For patients with large maximal bladder capacity, both treatment groups (alarm alone and alarm with retention control) 9 out of 10 patients became dry for 14 consecutive nights. For patients with small maximal bladder capacity in the group which had alarm treatment 10 out of 10 patients became dry for 14 nights compared to 9 out of 10 in the group which had alarm with retention control treatment. Change in number of wet nights: For patients with a large bladder capacity; the mean number of wet nights per week at end of treatment for the alarm group was 3.2 compared to 2.9 for the retention control and alarm group. At follow up the mean number of wet nights per week was 1.5 for the alarm group and 0 for the retention control and alarm group. For patients with a small bladder capacity; the mean number of wet nights per week at end of treatment for the alarm group was 3.4 compared to 3 for the retention control and alarm group. At follow up the mean number of wet nights per week was 1.7 for the alarm group and 1.3 for the retention control and alarm group. The study showed the relationship during treatment between maximal functional bladder capacity and change in number of wet nights was significant $F(1,33) = 4.90$ $p<0.03$, this relationship was also shown to be significant during followup $F(1,36) = 4.74$ $p<0.04$ Relapse: For patients with large maximal bladder capacity the group having alarm therapy alone had the smallest relapse rate (33%). The group having alarm with retention control had a 40% relapse rate.

	For patients with small maximal bladder capacity the group with alarm only had the largest relapse rate of the study (60%) where as the group having alarm with retention control had the smallest relapse rate (33%).
Safety and adverse effects	None reported
Does the study answer the question?	Overall 92.5% of all patients achieved 14 consecutive dry nights The study concluded that for patients with a small maximal bladder capacity there was some advantage to treating with alarm and retention control, but for patients with large maximal bladder capacity combining alarm with retention control was not more sucessful than alarm treatment alone.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies with same comparators.
Directly applicable to guideline population?	Children's age range was 5-13 years.
Internal Validity	Unclear allocation concealment and blinding

Houts AC;Peterson JK;Whelan JP;

Prevention of relapse in full-spectrum home training for primary enuresis

Ref ID 363 1986

Study Type	Randomised Controlled Trial	**Funding**	Faculty Research Grant from Memphis State University and from the Centre for Applied Phychological Research made avaliable through the Centers of Excellence Program of the State of Tennessee.

Number of participant	56 patients in total, 15 in group A (bell and pad treatment alone), 15 in group B (bell and pad treatment plus retention control training), 15 in bell and pad treatment plus retention control training and overlearning and 11 in the control group.
Inclusion/Exclusion Criteria	Inclusion: primary enuresis.
Patient Characteristics	In the treatment groups there were 35 males and 10 females. The mean age for the males was 8.35 (2.54 SD) years and for females was 9.06 (2.72 SD) and range for both was 5-13 years old. Most were wet every night and none had been dry for 2 or more months. In the control group the mean number of wet nights per week was 5.41 (1.63 SD). The groups (treatment and control) did not vary significantly in age, gender, socioeconomic status and family history of enuresis.
Recruitment	From paediatric referrals to the Memphis State University Enuresis Clinic and from media annoucements
Setting	At home, USA.
Interventions/ Test/ Factor being investigated	Group A: alarm with retention control training Group B: alarm Group C: control group - no treatment (waiting list)
Comparisons	Between groups A, B and C.
Length of Study/ Follow-up	1 year.

Outcome measures studied	Number of children achieving 14 dry consecutive nights, number not dry for 14 consecutive nights, drop outs and relapse.
Results	Duration of treatment was 16 weeks. 14 consecutive dry nights: 9 out of 15 children in the alarm only group achieved 14 nights dry compared with 13 out of 15 in alarm with retention control group and 0 out of 11 in the control goup. Drop out: 3 out of 15 children in the alarm only group dropped out compared with 2 out of 15 children in alarm with retention control group and 0 out of 11 children in the control group. Patients who failed to be dry for 14 nights tended to be older (mean = 9.58 years SD 3.22), drop outs tended to be younger (mean 6.88 years SD 1.5) compared with patients who achieved 14 dry nights (mean 8.58 years SD 2.57). Relapse: Relapse was defined as wet at least 1 night in each of 2 consecutive nights At 6 months: 3 out of 9 children in the alarm only group relapsed compared with 5 out of 13 in alarm with retention control group. At 1 year: 3 out of 9 children in the alarm only group relapsed compared with 6 out of 13 children in alarm with retention control group. There was a higher relapse rate in patients who had alarm with retention control compared to those who had alarm therapy alone (62% compared to 44%). However the authors state that having retention control therapy delayed the onset of relapse (mean - 9 days (SD 5.05) for alarm alone, 22.88 days (SD 26.13) for alarm and retention control) Relapse patients tended to be younger than those who did not relapse (mean 7.78 years SD 2.37 compared to 9.25 years SD 2.6; p <0.12).
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that patients were more likely to achieve 14 nights dry if they were treated with alarm and retention control (87% compared to 60% for alarm or alarm with retention control and over learning). The study also showed that patients were less likely to relapse if they were treated with alarm and retention control and over learning. Patients who had alarm only were less likely to relapse compared to those who had alarm and retention control
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies with same comparison.
Directly applicable to guideline population?	Yes age group was 5-13 years old.
Internal Validity	Unclear allocation concealment and blinding

Jehu D;Morgan RT;Turner RK;Jones A;

A controlled trial of the treatment of nocturnal enuresis in residential homes for children

Ref ID 156 1977

Study Type	Randomised Controlled Trial	**Funding**	Department of Health and Social Security and the City of Birmingham Social Services Committee.

Number of participant	39 patients in total: 19 in group A and 20 in group B.
Inclusion/Exclusion Criteria	Inclusion: aged over 4 years old, wetting at least 4 times a night, attending a normal school (not a special school), have not tried alarm treatment in the previous year, and no gross handicap.
Patient Characteristics	In the treatment froup there were 8 boys and 11 grils, in the control group there were 17 boys and 3 girls The mean age was 9 years and 4 months, (the range was 4 years and 9 months to 14 years and 7 months)
Recruitment	A survery of children in children's home under Birmingham City Social Services was carried out to identify children who met the criteria.
Setting	Children's home in Birmingham, UK.
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: control - no treatment
Comparisons	Between group A and B
Length of Study/ Follow-up	20 months
Outcome measures studied	Number of children achieving 14 consecutive dry nights, drop outs, mean number of dry nights, and number relapsing.
Results	Patients were treated with the alarm for 3-4 months, until success was achieved. 14 consecutive dry nights: In the alarm group 95% (18 out 19) achieved 14 dry nights compared to 0% (0 out of 20) in the control group. NB the child who failed had absconded from the children's home Relapse At 6 months 17% had relapsed (3 out of 18 children) Change in mean number of wet nights: The authors reported a signficant reduction in the number of wet nights for the treatment group ($F=16.5068$, $df = 11,187$, $p<0.001$) The mean number of wet nights for the control group was not significant ($F=0.9678$, $df = 11,209$, $p>0.05$) Drop outs: 1 child in the alarm group absconded from the childrens home and was treated a failure.
Safety and adverse effects	None reported.
Does the study answer the question?	The alarm group was treated until sucessful. Therefore 18 out of 19 children acieved 14 nights dry (1 child absconded from the nursing home) and there was a 17% relapse rate.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar results as to other studies comparing alarm to no treatment.
Directly applicable to guideline population?	Correct population - children were aged over 4 years old.
Internal Validity	Unclear allocation concealment and blinding

Kolvin I;Taunch J;Currah J;Garside RF;Nolan J;Shaw WB;

Enuresis: a descriptive analysis and a controlled trial

Study Type	Randomised Controlled Trial	**Funding**	Partially funded by Geigy

Number of participant	94 in total: 35 in group A, 32 in group B and 27 in group C.
Inclusion/Exclusion Criteria	Inclusion: aged between 8 and 10 years.
Patient Characteristics	The mean age was 9 years and 4 months. Most of the patients had poor toilet facilities, with 35 patients having out-door toilets the mean number of children per family was 3.9. 14 children had divorced parents. 44 patients had siblings who had had enuresis and 59 had family members who had had enuresis.
Recruitment	Through a survey of schools.
Setting	At home
Interventions/ Test/ Factor being investigated	Group A: imipramine Group B: alarm (pad and buzzer) Group C: placebo
Comparisons	Between groups A, B and C
Length of Study/ Follow-up	4 months.
Outcome measures studied	Mean number of wet nights.
Results	10% of patients were lost at 4 month follow up. The number of children who had greater than 80% improvement in number of dry nights: In the imipramine group 16 out of 35 children achieved a greater than 80% improvement in the number of dry nights compared to 17 out of 32 in alarm group. Mean number of wet nights at the end of treatment: In the imipramine group the mean number of wet nights was 2.3 (sd 3.5) compared to 2.3 (sd 3.2). Mean number of wet nights at follow up: In the imipramine group the mean number of wet nights at follow up was 3.35 (sd 3) compared to 2.3 (sd 2.3) in the alarm group.
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that the alarm group was slow to improve but maintained improvement after treatment was stopped. The imipramine group had a rapid improvement initially but a large decline after treatment was stopped. The placebo group's improvement was seen to remain after treatment was stopped.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies with same comparison.
Directly applicable to guideline population?	Children were aged between 8 and 10 years.
Internal Validity	Unclear allocation concealment and blinding

Ref ID 118 1987

Study Type	Randomised Controlled Trial	**Funding**	W. T. Grant Foundation of New York

Number of participant	121 in total, 66 in group A and 55 in group B
Inclusion/Exclusion Criteria	Inclusion: primary NE, aged 8-14 years, and parents were proficient in either French or English.
Patient Characteristics	Age range was 8-14 years and 7 patients had day-time urgency. The study reported there was no significant difference between the treatment group and control group in age, social class, sex, parental education, language and single parent families.
Recruitment	Patients were referred to the enuresis clinic of the Montreal Children's Hospital.
Setting	Montreal Children's hospital, Canada, and at home
Interventions/ Test/ Factor being investigated	Group A: conditioning alarm (Nytone Enuretic Alarm) continued until 14 consecutive dry nights were achieved. Then the "overlearning" procedure (which consists of having the child drink 3 to 4 glasses of liquid before bed) was followed until a further 14 consecutive nights occurred.Bladder control exercises and anticholinergic drugs were added for a few patients with daytime urgency who were not responding to conditioning after 3 months. Group B: control - no treatment
Comparisons	Between group A and B
Length of Study/ Follow-up	None.
Outcome measures studied	Number of children dry for 14 consecutive nights, adverse events, CBCL behaviour rating, and Piers-Harris Self Concept score.
Results	The mean treatment time for group A was 18.4 (SD5.8) weeks and for group B was 13.2 (SD 1.9). Dry for 14 nights: In group A (alarm) 42 out of 61 children (69%) became dry for 14 consecutive nights compared to 1 out of 55 children (2%) in group B (control). Adverse events: In group A (alarm) 4 children could not cope with the alarm. CBCL score: In group A (alarm) the baseline score was 60.1 and after treatment the mean score was 55.2. For group B (control) the baseline mean score was 61.2 and after treatment the mean score was 59.0. There was no significant difference (p=0.11) between the two groups with regard to changes. Piers-Harris Self-Concept score: In group A (alarm) the baseline score was 58.5, and after treatment the mean score was 61.5. For group B (control) the baseline mean score was 54.6 and after treatment the mean score was 53.7. There was a significant difference (p=0.04) in the two changes. The study also considered the changes to the CBCL and Piers-Harris scores relating to the success of treatment. The results showed that if treatment was successful there was a -5.2 change to the CBCL score compared to a change of -2.3 and -2.0 for >25% improvement and <25% improvement. For the Piers-Harris score there was a 3.2 change if the treatment was successful compared to 3.7 and 0.4 if the treatment was >25% improvement and <25% improvement.
Safety and adverse effects	4 patients in group A (alarm) could not cope with the alarm treatment

Does the study answer the question?	The study showed that treating children with an alarm was more effective in achieving 14 dry nights compared with no treatment. The study also showed that there was a significant difference in the change in Piers-Harris Self-Concept score, with those treated with an alarm having a greater mean improvement.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies comparing alarm to no treatment.
Directly applicable to guideline population?	Age range was 8-14 years.
Internal Validity	Unclear allocation concealment and blinding

Ozden C;Ozdal OL;Aktas BK;Ozelci A;Altinova S;Memis A;

The efficacy of the addition of short-term desmopressin to alarm therapy in the treatment of primary nocturnal enuresis

Ref ID 603 2008

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	52 in total: 30 in group A, 22 in group B.
Inclusion/Exclusion Criteria	Inclusion: primary monosymptomatic NE, aged between 6-15 years, and wetting at least 3 times a week. Exclusion: diurnal enuresis, UTI, polyuric disorders such as diabetes insipidus and diabetes mellitus, known history of renal disease, hypertension, genitourological abnormalities, mental retardation, neurological disease, use of diuretic drugs, or prior use of alarms or desmopressin therapy.
Patient Characteristics	54.5% were boys, the mean age was 10.1 (2.01 SD years) and the mean number of wet nights per week was 5.8 (1.4 SD). Age range was 6-15 years. Group A had a mean age of 9.9 (1.8 SD) years and the mean number of wet nights per week was 5.9 (1.5 SD). Group B had a mean age of 10.3 (2.2 SD) years and the mean number of wet nights per week was 5.7 (1.3 SD).
Recruitment	Not reported.
Setting	Turkey, treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm for 12 weeks in with 6 weeks ofadditional desmporessin Group B: alarm
Comparisons	Between group A and B
Length of Study/ Follow-up	24 weeks
Outcome measures studied	Change in number of wet nights. Numbers relapsing.
Results	6 weeks treatment Dry or 75% improvement in dry nights at 12 weeks: In group A (alarm and desmopressin) 22.2% (6 children) compared to 30.4% (7 children) in group B (alarm). Drop out: In group A (alarm and desmopressin) 3 out of 30 children dropped out compared to 5

	out of 22 children in group B (alarm), this was not significantly different (p>0.05). Change in mean number of wet nights: Before treatment group A (alarm and desmopressin) had a mean number of 5.9 (SD 1.5) wet nights and group B (alarm) had a mean number of 5.7 (SD 1.3). This difference was not significant. At 3 weeks group A (alarm and desmopressin) had a mean number of 2.7 (SD 0.5) and group B (alarm) had a mean number of 3.2 (SD 0.4), this difference was significant (p = 0.0001). At 6 weeks group A (alarm and desmopressin) had a mean number of 2.2 (SD 0.5) and group B (alarm) had a mean number of 2.7 (SD 0.6), this difference was significant (p = 0.004). At 12 weeks group A (alarm and desmopressin) had a mean number of 2.0 (SD 0.8) and group B (alarm) had a mean number of 1.8 (SD 0.54). This difference was not significant.
Safety and adverse effects	None reported.
Does the study answer the question?	There was no significant difference between patients receiving alarm and desmopressin compared to alarm alone in achieving 75% improvement in the number of dry nights or in becoming dry at 12 weeks. There was a significant difference in the mean number of wet nights at 3 weeks and 6 weeks with alarm and desmopressin therapy having significantly fewer wet nights compared to alarm therapy alone.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Age range was 6-15 years.
Internal Validity	Unclear allocation concealment and blinding

Ronen T;Wozner Y;Rahav G;

Cognitive intervention in enuresis

Ref ID 370 1992

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	77 in total: 19 in group A, 18 in group B (n=40 in the two groups which are not reported here: star charts and cognitive therapy.)
Inclusion/Exclusion Criteria	Inclusion: primary NE, and aged over 5 years Exclusion: medical problems in urinary system, or developmental problems.
Patient Characteristics	Mean age was 10.05 (2.28 SD) years, 51% were boys, and bed wetting was severe.
Recruitment	100 children applied and had been invited to take part in an initial intake session as part of of the regular agency procedure.
Setting	Israel, treatment was administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm (pad and bell) Group B: control group - no treatment, waiting list group The study also considered cognitive behaviour therapy and star charts with rewards which were not included as not relevant comparators
Comparisons	Between groups A and B
Length of Study/ Follow-up	1 year

Outcome measures studied	Number of children achieving 3 consecutive dry weeks. Also, mean number of wet nights in last 3 weeks.
Results	18 weeks treatment Dry for 21 nights: In group A (alarm) 12 out of 19 children (63%) became dry compared to 0 out of 18 (0%) in group B (control=no treatment). Drop out: In group A (alarm) 4 children (21%) dropped out compared to 2 children (11%) in group B (control). Mean number of wet nights per 3 weeks: In group A (alarm) the mean number of wet nights was 1.23 (sd 5.28) compared to 17.22 (SD 9) in group B (control).
Safety and adverse effects	None reported
Does the study answer the question?	There was no significant difference in the number of children becoming dry for 21 nights or in the change in mean number of wet nights between the patients receiving DBT and alarm and those receiving alarm therapy alone. However there were fewer relapses in the DBT and alarm group compared to the alarm group (15% compared to 60%)
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies comparing alarm and no treatment.
Directly applicable to guideline population?	Children were aged over 5 years.
Internal Validity	Unclear allocation concealment and blinding

Tuygun C;Eroglu M;Bakirtas H;Gucuk A;Zengin K;Imamoglu A;

Is second-line enuretic alarm therapy after unsuccessful pharmacotherapy superior to first-line therapy in the treatment of monosymptomatic nocturnal enuresis?

Ref ID 32 2007

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	84 patients in total: 35 in group A and 49 in group B.
Inclusion/Exclusion Criteria	Inclusion: monosymptomatic nocturnal enuresis, and wet at least 3 times a week during the last 3 months. Exclusion: Diurnal enuresis, polyuric disorders, genitourinary system abnormalities, neurological disorders, or recurrent UTI.
Patient Characteristics	The median age was 8 years (range 6-13 years). The ratio of male/ female was 3/2. There was no significant difference between the three group's age or sex. 71.73% had at least one parent with a history of enuresis. At baseline 54.34% were wet 25-30 nights a month, 20.65% were wet 20-25 nights a month and 25% were wet 15-20 nights a month.
Recruitment	Not reported.
Setting	Turkey, treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: desmopressin Group C was not included in this review as considers patients who had failed treatment.

Comparisons	Between treatment groups.
Length of Study/ Follow-up	6 months
Outcome measures studied	Number of children achieving >90% decrease in number of wet nights, 50-90% decrease in number of wet nights, relapse at 6 months, and change in number of wet nights.
Results	Treatment was for 3 months >90% decrease in number of wet nights: After 3 months of treatment in group A (alarm) 20 out of 35 children (57.14%) had achieved a >90% decrease in number of wet nights compared to 25 out of 49 (51.02%) in group B (desmopressin). These differences were not significant. 50-90% decrease in number of wet nights: After 3 months of treatment in group A (alarm) 9 out of 35 children (27.71%) had achieved a 50-90% decrease in number of wet nights compared to 15 out of 49 (30.61%) in group B (desmopressin). These differences were not significant. Relapse at 6 months: At 6 months, in group A, 10 out of 35 children (28.57%) had relapsed compared to 27 out of 49 (55.10%) in group B (desmopressin). The difference between groups A and B was significant p=0.008. Change in mean number of wet nights: In group A (alarm) at baseline the mean number of wet nights per month was 23.2 (SD 6.23) and at the end of treatment it was 3.41 (SD7.68). This difference was significant p<0.001. In group B (desmopressin) at baseline the mean number of wet nights per month was 23.44 (SD 6.3) and at the end of treatment it was 10.7 (SD 10.94), this difference was significant p<0.001. The difference between groups A and B was also significant.
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that treating children with an alarm was more effective than desmopressin in reducing the number of wet nights. The study showed that few children who were treated with an alarm were significantly less likely to relapse than those treated with desmopressin. All groups had a significant reduction in the mean number of wet nights per month.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies comparing desmopressin and alarm.
Directly applicable to guideline population?	Children were aged between 6-13 years.
Internal Validity	Unclear allocation concealment and blinding

van Londen A;van Londen-Barentsen MW;van Son MJ;Mulder GA;

Arousal training for children suffering from nocturnal enuresis: a 2 1/2 year follow-up

Ref ID 338 1993

Study Type	Randomised Controlled Trial	**Funding**	Not reported.

Number of participant	127 in total, 38 in group A, 39 in group B and 36 in group C.
Inclusion/Exclusion Criteria	Inclusion: aged between 6-12 years

Patient Characteristics	The mean age was 8.6 years, 70% were boys, and 87% had primary NE.
Recruitment	Not reported.
Setting	Netherlands, treatment at home
Interventions/ Test/ Factor being investigated	Group A: alarm with reward stickers for correct behaviour Group B: alarm with reward stickers for dry nights and punishment sticker for wet nights Group C: alarm
Comparisons	Between groups A, B and C.
Length of Study/ Follow-up	2.5 years
Outcome measures studied	Number of children dry for 14 consecutive nights, and numbers relapsing.
Results	20 weeks treatment Dry at 14 nights: In group A (alarm with reward stickers for correct behaviour) 37 out of 38 children achieved 14 dry nights compared to 33 out of 39 in group B (alarm with reward sticker for dry nights and punishment sticker for wet nights) and 26 out of 36 in group C (alarm alone). These differences were significant when comparing group A to group B (binomal test P<0.001) and group (binomal test P<0.000). Relapse at 2.5 years follow up: In group A (alarm with reward stickers for correct behaviour) 10 out of 37 had relapsed at the end of 2.5 years follow up compared to 30 out of 33 in group B (alarm with reward sticker for dry nights and punishment sticker for wet nights) and 13 out of 26 in group C (alarm alone).
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that giving a child an alarm with reward stickers for correct behaviour was significantly more sucessful in achieving 14 dry nights compared to giving a child an alarm with reward stickers for dry nights and punishment sticker for wet nights or an alarm alone.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Age range is 6-12 years.
Internal Validity	Unclear allocation concealment and blinding.

Wagner W;Johnson SB;Walker D;Carter R;Wittner J;

A controlled comparison of two treatments for nocturnal enuresis

Ref ID 143 1982

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant 49 in total, 12 in each group

Inclusion/Exclusion Criteria	Inclusion: aged 6-16 years, IQ greater than 70, primary NE, no physcial or neurological disorders, wet at least 3 times a week, no treatment for NE in previous year, and agreed to be randomised. Exclusion: day time wetting.
Patient Characteristics	The mean age was 7.9 years. The baseline % of nights wet for group A (alarm) was 75%, group B (imipramine) 77.33% and group C (waiting list) 64.33%, there was no signficant difference in the baseline wetting %.
Recruitment	From local paediatric clinics and private physicians, adverts in newspapers and on TV, and contact with local schools.
Setting	Florida, USA, treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm (pad and bell) Group B: imipramine Group C: control - no treatment, waiting list
Comparisons	Between groups A, B and C.
Length of Study/ Follow-up	6 months.
Outcome measures studied	Number of children achieving 14 consecutive dry nights,% of wet nights, and relapse rates.
Results	14 weeks treatment Dry for 14 consecutive nights: In group A (alarm) 10 out of 12 children, 83% achieved dryness for 14 consecutive nights compared to 4 out of 12 children, 33% in group B (imipramine) and 1 out of 12 children, 8% in group C (waiting list) % of wet nights: The study showed that by the final treatment week, group A was significantly more sucessful than B and C (8.25% compared to 39.25% and 60.83%). In the final week of treatment the mean number of wet nights for children with alarm treatment was 0.58 and for children with imipramine was 2.75. Relapse: Relapse was defined as 3 wet nights in a 2 week period. Of the children who achieved 14 dry nights dry in group A (alarm) 5 out of 10 children (50%) relapsed compared to 4 out of 4 children (100%) in group B (imipramine) and 100% in group C (waiting list).
Safety and adverse effects	None reported
Does the study answer the question?	The study showed that giving a child an alarm was more sucessful than imipramine and a control waiting list group in achieving 14 dry nights (83% compared to 33% and 8%). The study also showed that the patients receiving alarm therapy had only a 50% relapse rate compare to 100% in both the imipramine group and waiting list group.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies with same comparison.
Directly applicable to guideline population?	Age range 6-16 years.
Internal Validity	Unclear allocation concealment and blinding

Wagner WG;Matthews R;

The treatment of nocturnal enuresis: a controlled comparison of two models of urine alarm

Study Type	Randomised Controlled Trial	**Funding**	Research Development Grant from the University of Southern Mississippi.

Number of participant	39 in total: 13 in each of the 3 groups.
Inclusion/Exclusion Criteria	Inclusion: primary NE, aged 5-16 years, IQ of greater than 70, no pyhsical or neurological disorder, wet at least 3 times a week, not had treaetment for NE in previous year, agree to randomisation Exclusion: day time wetting
Patient Characteristics	The mean age was 7.9 years. 51% were male and 95% were white. Baseline % of wet nights per week for group A (contiguous alarm) was 80.15%, for group B (delayed alarm) 83.46%, for group C (waiting list) 90.15%.
Recruitment	Not reported
Setting	Mississippi, USA, treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: control group - no treatment, waiting list The study also considered an alarm with a 3 second delay which was not a relevant comparator and was not included in the review
Comparisons	Between groups A and B.
Length of Study/ Follow-up	6 months.
Outcome measures studied	Number of children achieving 14 consecutive dry nights, change in number of wet nights, and relapse.
Results	12 weeks treatment Dry for 14 consecutive nights: In group A (alarm) 8 out of 13 children (62%) achieved dryness for 14 consecutive nights compared to 1 out of 13 children (8%) in group B (waiting list). There was a signficant difference between the alarm group and the waiting list group ($P < 0.01$) % of wet nights: The study showed that by the final treatment week, group A was significantly more sucessful than B (5.38% compared to 72.90%). Relapse: Of the children who achieved 14 dry nights in group A (alarm) 2 out of 8 relapsed compared to 1 out of 1 in group B (waiting list). The study showed the alarms did malfunction.
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that alarms were more sucessful than waiting lists in achieving 14 dry nights (62% compared to 8%). The study showed there was a significant difference between the alarm group and the waiting list group.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies comparing alarm to no treatment.
Directly applicable to guideline population?	Age range 5-16 years.

Internal Validity Unclear allocation concealment. Single blinded.

Wille S;

Comparison of desmopressin and enuresis alarm for nocturnal enuresis

Ref ID 127 1986

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	50 patients recruited: 25 allocated to each of the two arms.
Inclusion/Exclusion Criteria	Inclusion: older than 6 years, not dry for more than 6 months since 3 years, wet at least 3 times a week, and able to give written and informed consent. Exclusion: treatment for NE in previous years, day time wetting, cardiovascular disease, renal disorder, neurological disorder, or chronic UTI.
Patient Characteristics	Group A had a mean number of wet nights at baseline line of 2.1. Group B had a mean number of wet nights at baseline line of 1.9.
Recruitment	Patients referred to S. Wille's clinic
Setting	Sweden, treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A:intranasal desmopressin Group B: alarm
Comparisons	Between groups A and B
Length of Study/ Follow-up	3 months
Outcome measures studied	Number of children dry for 14 consecutive nights, relapse rates, change in number of wet nights, and adverse events.
Results	3 months treatment Success of being dry for 28 days with only 5 wet nights or achieving a lower wetting score (score: very wet = 3, a little wet = 2, dry = 1): In group A (desmopressin) 17 out of 24 children became dry compared to 19 out of 22 in group B (alarm). The study stated that at the end of treatment both groups were significantly drier than before the treatment however the alarm group was more successful (alarm $p<0.001$; desmopressin $p<0.02$). There was no significant difference between group A (desmopressin) and group B (alarm). Group A (desmopressin) had significantly more dry nights than group B (alarm) during the first 3 weeks ($p<0.001$) however during the last 9 weeks of treatment the alarm group had more dry nights, and significantly more in the 11th week ($p<0.002$). The study stated that due to the high relapse rate in the desmopressin group, over all during the first 2 weeks of treatment and at the 3 month follow up the alarm group was significantly better than the desmopressin group ($p<0.02$, $p<0.001$, 2 weeks and 3 months respectively) The mean number of wet nights per week at end of treatment for the alarm group was 1.1 (SD 1.88) compared to 2.1 (SD 1.96) for the desmopressin group. Relapse: 1 patient in the alarm group relapsed in the 3 month follow up compared to 10 in the desmopressin group. Drop out: 1 child from the alarm group dropped out due to lack of improvement Adverse events: In the alarm group 78% had false alarms, 19% said the alarm did not work when the child was wet, 56% said the alarm did not wake the child, 56% said the alarm woke

	other family members instead and 1 patient was afraid of the alarm. In the desmopressin group 13% reported nasal discomfort, 3% had occasional nose bleeds and 5% experienced a bad taste in the throat. The study included a cross over of treatments for children who were unsuccessful in their original treatment group. Of the children who changed from desmopressin to alarm 2 children improved by a 2 month follow up, 3 were better than before and 5 did not respond. Of the children who changed from alarm to desmopressin 2 children did improve but subsequently relapsed. There was no significant difference between the cross over results.
Safety and adverse effects	In the alarm group 78% had false alarms, 19% said the alarm did not work when the child was wet, 56% said the alarm did not wake the child, 56% said the alarm woke other family members instead and 1 patient was afraid of the alarm. In the desmopressin group 13% reported nasal discomfort, 3% had occasional nose bleeds and 5% experienced a bad taste in the throat.
Does the study answer the question?	The study showed that both alarm treatment and desmopressin lead to a significant reduction in the number of wet nights. The study showed that alarm treatment was more successful in achieving 28 dry nights (with less than 5 wet nights) than desmopressin, however this difference was not significant until the high relapse rate of desmopressin was taken into account. With alarms then being significantly more effective. The desmopressin group had a higher relapse rate than the alarm group. More patients receiving alarm therapy reported side effects than those receiving desmopressin.
Effect due to factor in study?	Yes (NB there is a 15% spontaneous cure rate associated with NE)
Consistency of results with other studies?	Similar to other studies comparing alarm to desmopressin
Directly applicable to guideline population?	Patients were aged over 6 years
Internal Validity	Unclear allocation concealment and blinding.

Grading: 2-	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

Baller WR;Giangreco CJ;

Correction of nocturnal enuresis in deaf children

Ref ID 3906 1970

Study Type Cohort **Funding** The alarms were provided by the Enurtone Company, Minneapolis, the consultant also worked for this company.

Number of participant	21 children
Inclusion/Exclusion Criteria	Deaf children with persistent bed wetting at Iowa School for the Deaf at Council Bluffs Iowa.
Patient Characteristics	15 boys and 6 girls, with age range 7 to 16 years.
Recruitment	At school.
Setting	Iowa School for the Deaf at Council Bluffs Iowa.
Interventions/ Test/ Factor being investigated	Light alarm.
Comparisons	No comparison.
Length of Study/ Follow-up	2 1/2 years follow up
Outcome measures studied	Numbers of children completely dry, and numbers relapsing.
Results	Only 2 or 3 children could be given the alarm at a time, with treatment for on average 3 weeks. Therefore there was over a year between the first and last child being treated. The alarm was a pad and bell device with a light which had a cone shaped shade to shine the light directly at the child's face. Children were given an explanation of the treatment by a consultant. All children (21) gained complete dryness (10 consecutive dry nights) within 30 nights (the paper states this is the normal time for a hearing child to become dry with a bell only alarm). One child relapsed but after 2 more treatments with the light alarm he gained dryness. After 2 1/2 year follow up, it was noted that the other 19 children at the school who wet the bed had also become dry within 3 months of the children in the trial. The study also noted that there were no undesirable side effects or unfavourable behaviour of the children in the trial.
Safety and adverse effects	None
Does the study answer the question?	The study showed all children treated with the light alarm became dry.
Effect due to factor in study?	Yes, although it should be noted that all other children at the school who wet the bed also became dry.

Consistency of results with other studies?	Not other studies considering deaf children treated with an alarm.
Directly applicable to guideline population?	Deaf children aged 7 to 16 years.
Internal Validity	Not addressed

Question: What is the clinical and cost effectiveness of desmopressin (nasal, tablets and melts) for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Burke JR;Mizusawa Y;Chan A;Webb KL;

A comparison of amitriptyline, vasopressin and amitriptyline with vasopressin in nocturnal enuresis.

Ref ID 325 1995

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	45 in total: 14 in Group A (amitriptyline), 17 in Group B (desmopressin), and 14 in Group C (desmopressin and amitriptyline)
Inclusion/Exclusion Criteria	Inclusion: 6-17 years, at least 3 wet nights a week for preceding 3 month period or not dry for more than 6 months. Exclusion: organic causes of NE, enuresis treatment in previous 6 months, neurogenic disorder, UTI, abnormal urinalysis haemotology or blood biochemistry, or concomitant medication known to interfere with study medication.
Patient Characteristics	In group A the mean age was 8.6 (SD 2.4) years, the mean wet nights per week was 5.8 (SD 0.9) In group B the mean age was 8.9 (SD 2.5) years, the mean wet nights per week was 6.0 (SD 0.9) In group C the mean age was 8.9 (SD 2.4) year, the mean wet nights per week was 6.3 (SD 0.9)
Recruitment	Not reported
Setting	Australia
Interventions/ Test/ Factor being investigated	Group A: amitriptyline hydrocholoride (25 mg or 50mg) Group B: intranasal desmopressin (20 micro grams) Group C: desmopressin and amitriptyline
Comparisons	Between treatment groups
Length of Study/ Follow-up	12 weeks
Outcome measures studied	Number of children cured, drop outs, and the mean number of wet nights at end of treatment and follow up.
Results	16 weeks of treatment Number of children cured: In Group A (amitriptyline) 3 out of 14 became dry, compared to 1 out of 17 in Group B (desmopresisn) and 4 out of 14 in Group C (desmopresisn and amitriptyline). Number of drop outs: In Group A (amitriptyline) 0 out of 14 dropped out, in Group B (desmopresisn) 3 out of 17 dropped out, and in Group C (desmopresisn and amitriptyline) 3 out of 14 dropped out. Mean number of wet nights per week at end of treatment: The mean number of wet nights per week for Group A (amitriptyline) was 3.3 (SD 1.9), for group B (desmopressin) mean was 4.7 (SD 1.7) and for Group C (desmopressin and amitriptyline) mean was 3.3 (SD 2.5) nights. Mean number of wet nights per week at 12 week follow up: The mean number of wet nights per week for Group A (amitriptyline) was 3.9 (SD 2.9), for Group B (desmopresisn) mean was 3.8 (SD 1.9) nights and for Group C (desmopressin and amitriptyline) it was 5.1 (SD 3.2) nights.
Safety and adverse effects	None reported

Does the study answer the question?	The study showed that more children became dry when treated with amitriptyline and desmopressin and amitriptyline alone. Patients treated with amitriptyline alone and with desmopressin and amitriptyline had fewer wet nights during treatment but at follow up patients in the desmopressin only group or amitriptyline only group had the fewest number of wet nights.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Not clear.
Directly applicable to guideline population?	Aged 6-17 years
Internal Validity	Trial was stopped early

Longstaffe S;Moffatt ME;Whalen JC;

Behavioral and self-concept changes after six months of enuresis treatment: a randomized, controlled trial

Ref ID 71 2000

Study Type	Randomised Controlled Trial	**Funding**	National Health Research and Development Program and Fering Inc

Number of participant	182 in total, 61 in group A, 60 in group B, 61 in group C.
Inclusion/Exclusion Criteria	Inclusion: aged over 7 years, monosyptomatic NE, wetting at least 12 times in a 4 week period, normal urinalysis, no history of fecal soiling and signs of normal bladder functioning. Exclusion: neurological or developmental abnormalities, diabetes insipidus, diabetes mellitus, chronic renal disease, history of constipation, or already having desmopressin or alarm therapy.
Patient Characteristics	In group A (alarm): 78.7% were male, 37.7 % were first born, 13.4% had a past history of UTI, 24.6% had a history of constipation. 94.9% had tried fluid restriction, 90% had tried lifting, 53.3% had tried behavioural techniques, 3.4% had tried bladder exercises, 20% had tried alarms, 13.3% had tried desmopressin, 14.3% had tried imipramine, 10.9% had tried oxybutnin. 36.2% had family history of NE on both sides, 41.4% had family history of NE on one side. In group B (intranasal desmopressin): 75% were male, 41.7% were first born, 6.7% had a past history of UTI, 23.3% had a history of constipation. 90% had tried fluid restriction, 86.7% had tried lifting, 58.3% had tried behavioural techniques, 11.7% had tried bladder exercises, 18.3% had tried alarms, 21.7% had tried desmopressin, 16.7% had tried imipramine, 8.6% had tried oxybutnin. 41.7% had family history of NE on both sides, 41.7% had family history of NE on one side. In group C (placebo): 61.7% were male, 34.5 % were first born, 13.8% had a past history of UTI, 21.4% had a history of constipation. 91.7% had tried fluid restriction, 95% had tried lifting, 67.8% had tried behavioural techniques, 19% had tried bladder exercises, 23.3% had tried alarms, 18.3% had tried desmopressin, 15.5% had tried imipramine, 8.6% had tried oxybutnin. 45.6% had family history of NE on both sides, 33.3% had family history of NE on one side.
Recruitment	Phycisian adverts, newspaper adverts, and posters and radio.
Setting	Treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: intranasal desmopressin Group C: placebo
Comparisons	Between group A, B and C

Length of Study/ Follow-up	6 months
Outcome measures studied	Number of patients having 14 dry nights. Self concept.
Results	14 consecutive dry nights: In group A (alarm) 35 children (57%) achieved 14 dry nights compared to 29 children (48%) in group B (desmopressin) and 23 children (38%) in group C (placebo). Drop out: 17 children in total dropped out 8 were from group A (alarm), 5 from group B (desmopressin) and 4 from group C (placebo) Behavioural changes: The behavioural changes were not related to the type of treatment or success of treatment, however there were significant positive changes in intellectual, physical appearance, anxiety, popularity (analysed through the Piers-Harris Subscales), there were also significant positive results on the Achenbach CBCL, Internalizing and Externalizing Behaviour Scores and Social, Thought and Attention Problems Subscales.
Safety and adverse effects	None reported.
Does the study answer the question?	There was no significant difference in the number of children achieving 14 consecutive dry nights between those receiving alarm and those receiving desmopressin. However more children became dry in the two treatment groups compared to the placebo group. The study also reported a positive change in the children's behaviour; however this was not related to treatment type or outcome success.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies with same comparisons.
Directly applicable to guideline population?	Children were aged over 7 years.
Internal Validity	Unclear blinding

Ng CFN;Wong SN;Hong Kong Childhood Enuresis Study Group.;

Comparing alarms, desmopressin, and combined treatment in Chinese enuretic children

Ref ID 369 2005

Study Type	Randomised Controlled Trial	**Funding**	Hong Kong Paediatric Nephrology Society with a research grant from Ferring Pharmaceuticals Limited

Number of participant	105 in total, 35 in Group A, 38 in Group B, 32 in Group C.
Inclusion/Exclusion Criteria	Inclusion: Primary NE, age range 7-15 years, and wetting at least 3 times a week in baseline 2 weeks. Exclusion: UTI in previous 3 months, day time wetting, polyuric disorders, abnormal urinanalysis, renal disease, previous diuretics, unwilling to be randomised, or previous treatment of alarms, desmopressin or tricyclics.
Patient Characteristics	The mean age was 9.5 (1.8 SD) years, and age range 7-12 years In Group A (alarm) the mean age was 9.5 (1.8 SD) years, 57% children were in the age range 7-9 years, 40% in 10-12 years and 3% in 13-15 years. 63% were boys, and the mean baseline number of wet nights a week was 5.1 (1.5 SD).

	In Group B (desmopressin) the mean age was 9.2 (1.8 SD) years, 69% children were in the age range 7-9 years, 26% in 10-12 years and 5% in 13-15 years. 68% were boys, and the mean baseline number of wet nights a week was 5.3 (1.4 SD). In Group C (alarm with desmopressin) the mean age was 9.8 (1.2 SD) years, 50% children were in the age range 7-9 years, 47% in 10-12 years and 3% in 13-15 years. 66% were boys, and the mean baseline number of wet nights a week was 4.9 (1.2 SD).
Recruitment	Patients presenting to 9 public hospitals in Hong Kong with primary NE.
Setting	Hong Kong and treatment administered at home.
Interventions/ Test/ Factor being investigated	Gourp A: alarm Group B: oral desmopressin Group C: alarm with oral desmopressin
Comparisons	Between groups A, B and C.
Length of Study/ Follow-up	12 weeks.
Outcome measures studied	Number of children dry for 14 consecutive nights, change in number of wet nights, adverse events, drop out, and relapse.
Results	Dry for 14 consecutive nights: In Group A (alarm) 8 out of 15 children achieved 14 dry nights, compared to 16 out of 38 children in Group B (desmopressin) and 20 out of 32 children in Group C (alarm and desmopressin). This difference was significant p = 0.014. Mean number of dry nights: In Group A (alarm) the mean number of dry nights was 2.8 (sd 2.2) compared to 2.7 (sd 2.4) in Group B (desmopressin) and 1.3 (sd 1.9) in Group C (alarm and desmopressin). Drop out: 12 children dropped out in total, 7 (20%) from Group A (alarm), 2 (5%) from Group B (desmopressin) and 3 (9%) from Group C (alarm and desmopressin). Relapse: In the alarm group (A) 0 out of 8 children relapsed at 3 months, compared to 9 out of 16 in the desmopressin group (B) and 7 out of 20 in the alarm with desmopressin group ©.
Safety and adverse effects	None
Does the study answer the question?	The study showed that significantly more patients achieved 14 consecutive dry nights if they were treated with alarm or desmopressin alone (71% compared to 42.9% and 52.6%.) The study also showed that there was a significant difference between groups in the % reduction of wet nights during the last 4 weeks of treatment and during the first 4 weeks of follow up, with patients being treated with alarm and desmopressin being significantly more successful than alarm or desmopressin alone.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies with same comparison.
Directly applicable to guideline population?	Age range was 7-15 years.
Internal Validity	Unclear blinding

Schulman SL;Stokes A;Salzman PM;

The efficacy and safety of oral desmopressin in children with primary nocturnal enuresis

Ref ID 176 2001

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	193 in total; of the 187 patients who completed the dose ranging phase of the study (phase 1), 148 continued into the dose titration phase (trial 2).
Inclusion/Exclusion Criteria	Inclusion: at least 3 wet nights a week, informed consent, no treatment in previous 30 days, and aged 6-16 years. Exclusion: organic causes of NE, day time wetting, organic urological disease, diabetes insipidus, UTI, known hypersensitivity to desmopressin, antibiotics, diuretics, or hyperactivity.
Patient Characteristics	Trial 1: 133 out of 193 were male, mean baseline wetting in 2 weeks in group A was 11 days (range 5-14), in group B 10 days (range 4-14), in group C 10 days (range 6-14),and in group D 10 days (range 6-14).
Recruitment	Not reported.
Setting	16 centres in USA.
Interventions/ Test/ Factor being investigated	Trial 1: Group A: 0.2 mg oral desmopressin Group B: 0.4 mg oral desmopressin Group C: 0.6 mg oral desmopressin Group D: matching placebo
Comparisons	Between treatment groups.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Number of children achieving 14 consecutive dry nights, mean number of wet nights, drop outs, and adverse events.
Results	2 weeks of treatment Trial 1: Mean number of wet nights during 2 week treatment: In group A (0.2 mg desmopressin) the mean number of wet nights was 4 (SD 1.33), in group B (0.4 mg desmopressin) mean was 3.5 (SD 1.73),and in group C (0.6 mg desmopressin) mean was 4.5 (SD 1.37). Number who ahcieved 14 consecutive dry nights: In group A (0.2 mg desmopressin) 2 out of 44 children achieved 14 consecutive dry nights compared to 6 out of 48 in group B (0.4 mg desmopressin), 3 out of 49 in group C (0.6 mg desmopressin) and 0 out of 49 in group D (placebo). Drop outs: 6 in total: due to non compliance, consent withdrawn, and failure to keep diary. Adverse events (1 or more per child): 43 out of 143 on desmopressin and 13 out of 48 on placebo had headache, increased cough, and abdominal pain. The authors reported these were unrelated to treatment and were resolved by end of trial.
Safety and adverse effects	Headache, abdominal pain, increased cough, phinitis, pharyngitis, infection and fever.
Does the study answer the question?	Study showed desmopressin was more effective than placebo.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies with same comparisons.

Directly applicable to guideline population?	Age range of 5 to 14 years.
Internal Validity	Unclear allocation concealment

Skoog SJ;Stokes A;Turner KL;

Oral desmopressin: a randomized double-blind placebo controlled study of effectiveness in children with primary nocturnal enuresis

Ref ID 284 1997

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	153 in total, data no avaliable for 6 so 147 in total. Group A desmopressin 200mcg n=37, Group B desmopressin 400mcg n=35, Group C desmopressin n=37 and Group D placebo n=38.
Inclusion/Exclusion Criteria	Inclusion: primary NE, and wet at least 3 times a week for 2 weeks. Exclusion: organic causes of NE, day time wetting, organic urological disease, diabetes insipidus, UTI all within previous 3 months, previous non-response (less than 50% decrease in wet nights) to desmopressin, hypersensitivity to desmopressin, clinically significant disease that would interfere with study, ongoing systematic antibiotic use, use of diuretics or any drug affecting urinary concentration, or medical treatment for hyperactivity.
Patient Characteristics	112 out of 147 were male and the mean age was 9.1 years (range 5-17 years).
Recruitment	Not reported
Setting	14 centres in USA
Interventions/ Test/ Factor being investigated	Group A (37): 200 micro grams oral desmopressin Group B (35): 400 micro grams oral desmopressin Group C (37): 600 micro grams oral desmopressin Group D (38): placebo
Comparisons	Between treatment groups
Length of Study/ Follow-up	None
Outcome measures studied	Mean number of wet nights in last 2 weeks,number dry for 14 nights, adverse events, and drop out rate.
Results	6 weeks of treatment Mean number of wet nights during last 2 weeks of trial In Group A (200 micro grams desmopressin 33 patients) the mean was 4 (SD 1.15), in Group B (400 micro grams desmopressin 33 patients) the mean was 3.5 (SD 1.44), in Group C (600 micro grams desmopressin 33 patients) the mean was 3.5 (SD 1.15) and in Group D (placebo 36 patients) the mean was 5 (SD 1.2). Number of children who achieved 14 consecutive dry nights: In Group A (200 micro grams desmopressin) 1 out of 33 achieved 14 consecutive dry nights compared to 4 out of 33 in Group B (400 micro grams desmopressin), 2 out of 33 in Group C (600 micro grams desmopressin) and 0 out of 36 in Group D (placebo). Adverse events: 66 out of 109 children on desmopressin experienced adverse events compared to 21 out of 38 on placebo (rhinitis, headache,pharyngitis, infection, cough all mild or moderate, there were 3 serious events on desmopressin where children withdrew from trial - 2 vomiting, 1 atopic dermatitis) Drop outs: 12 out of 147 discontinued trial.

Safety and adverse effects	Vomiting, atopic dermatitic, rhinitis, headache,pharyngitis, infection, and cough.
Does the study answer the question?	The study shows that more children become dry with desmopressin than placebo and 400 micro grams was most effective although there was little difference between the 3 doses.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies with same comparisons.
Directly applicable to guideline population?	Children were age 5-17 years.
Internal Validity	Unclear allocation concealment

Tuygun C;Eroglu M;Bakirtas H;Gucuk A;Zengin K;Imamoglu A;

Is second-line enuretic alarm therapy after unsuccessful pharmacotherapy superior to first-line therapy in the treatment of monosymptomatic nocturnal enuresis?

Ref ID 32 2007

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	84 patients in total: 35 in Group A, 49 in Group B.
Inclusion/Exclusion Criteria	Inclusion: monosymptomatic nocturnal enuresis and wet at least 3 times a week during the last 3 months. Exclusion: Diurnal enuresis, polyuric disorders, genitourinary system abnormalities, neurological disorders, or recurrent UTIs.
Patient Characteristics	The median age was 8 years (range 6-13 years). The ratio of male/ female was 3/2. There was no significant difference between the three group's age or sex. 71.73% had at least one parent with a history of enuresis. At baseline 54.34% were wet 25-30 nights a month, 20.65% were wet 20-25 nights a month and 25% were wet 15-20 nights a month.
Recruitment	Not reported.
Setting	Turkey, treatment administered at home.
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: desmopressin Group C was not included as these are patients who failed first line treatment
Comparisons	Between groups A and B.
Length of Study/ Follow-up	6 months
Outcome measures studied	Number of children with >90% decrease in number of wet nights, 50-90% decrease in number of wet nights, relapse at 6 months, and change in number of wet nights.
Results	Treatment was for 3 months >90% decrease in number of wet nights: After 3 months of treatment in Group A (alarm) 20 out of 35 children (57.14%) had achieved a >90% decrease in number of wet nights compared to 25 out of 49 (51.02%) in Group B (desmopressin). These differences were not significant. 50-90% decrease in number of wet nights: After 3 months of treatment in Group A (alarm) 9 out of 35 children (27.71%) had achieved a 50-90% decrease in number of wet nights compared to 15 out of 49 (30.61%) in Group B (desmopressin). These differences were not significant.

Relapse at 6 months:
At 6 months 10 out of 35 children (28.57%) in Group A had relapsed compared to 27 out of 49 (55.10%) in Group B (desmopressin). The difference between Groups A and B was significant p=0.008.

Change in mean number of wet nights:
In Group A (alarm) at baseline the mean number of wet nights per month was 23.2 (SD 6.23) and at the end of treatment it was 3.41 (SD 7.68). This difference was statistically significant p<0.001. In Group B (desmopressin) at baseline the mean number of wet nights per month was 23.44 (SD 6.3) and at the end of treatment it was 10.7 (SD 10.94). This difference was statistically significant(p<0.001). The difference between Groups A and B was also statistically significant.

Safety and adverse effects None reported.

Does the study answer the question? The study showed that treating children with an alarm was more effective than desmopressin in reducing the number of wet nights. The study showed that few children who were treated with an alarm were significantly less likely to relapses than those treated with desmopressin. All groups had a significant reduction in the mean number of wet nights per month.

Effect due to factor in study? Yes.

Consistency of results with other studies? Similar to other studies with same comparison.

Directly applicable to guideline population? Children were aged between 6-13 years.

Internal Validity Unclear allocation concealment

Yap HK;Chao SM;Tan AY;Murugasu B;Ong EK;Low EH;

Efficacy and safety of oral desmopressin in the treatment of primary nocturnal enuresis in Asian children

Ref ID 271 1998

Study Type Randomised Controlled Trial **Funding** Supported by Ferring Pharmaceuticals Limited.

Number of participant 37 children in crossover trial.

Inclusion/Exclusion Criteria Inclusion: primary monosymptomatic nocturnal enuresis.
Exclusion: no current enuresis treatment.

3 excluded because data incomplete.

Patient Characteristics 22 boys.
Aged between 7 and 18 years.
Minimum frequency of wetting 6 nights or more during a 2 week observation period.
Free of diurnal incontinence, and were not on any specific treatment for enuresis prior to sutyd entry.

Recruitment From three participating Paediatric Departments: National University Hospital, Singapore General Hospital and Tan Tock Seng Hospital.

Setting Hospital clinic, Singapore.

Interventions/ Test/ Factor being investigated A: (34) desmopressin 400mg oral;.
B: (34) Placebo.
Duration of treatment 5 weeks, 2 week washout.

Comparisons Between treatment and placebo. Crossover trial.

Length of Study/ Follow-up	2 weeks post-treatment period.
Outcome measures studied	Average number of wet nights per week; no. of children where average number of wet nights decreased to less than 3 per week.
Results	5 weeks of treatment with a 2 week wash out period Number achieving 14 dry nights: A=23/34; B=7/34. Wet nights after trial (mean, SD): A= 2.5 (2.7), B=4.5 (2.1).
Safety and adverse effects	None reported
Does the study answer the question?	The author concludes that oral desmopressin is a safe and efficacious drug for the short-term treatment of children with primary nocturnal enuresis.
Effect due to factor in study?	No.
Consistency of results with other studies?	Similar to other studies comparing desmopressin to placebo.
Directly applicable to guideline population?	Yes.
Internal Validity	Unclear allocation concealment

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Birkasova M;Birkas O;Flynn MJ;Cort JH;

Desmopressin in the management of nocturnal enuresis in children: a double-blind study

Ref ID 494 1978

Study Type	Randomised Controlled Trial	**Funding**	AM 10080 grant from the National Institutes of Health, the Life Sciences Foundation, Inc and the Czechoslovak Academy of sciences.

Number of participant	22 in total. Crossover trial.
Inclusion/Exclusion Criteria	Inclusion: failed to respond to psychotherapy and fluid restriction regime. Exclusion: organic causes.
Patient Characteristics	14 out of 22 children were boys. The mean age was 6.6 (SD 2.9) years (range 4-12 years). Mean baseline wetting in 2 weeks was 10.6 (SD 4.9) nights.
Recruitment	Not reported.
Setting	New York, USA.
Interventions/ Test/ Factor being investigated	Group A (17 patients): 10 µg intranasal desmopressin Group B (5 patients): 40 µg intranasal desmopressin Group C: placebo
Comparisons	Between groups A, B and C
Length of Study/ Follow-up	4-6 weeks
Outcome measures studied	Mean number of wet nights per fortnight, and number becoming totally dry.
Results	2 weeks of treatment Number of wet nights per fortnight: Groups A and B had a combined mean of 4.2 (SD 4.5) compared to group C which had a mean of 11 (SD 4.4). Number who became totally dry: 5 patients receiving a higher dosage were totally dry. 5/6 patients were dry without treatment. 9 continued desmopressin single blind for 4 to 6 weeks then given placebo 7 remained dry without drug 1 wet once monthly and 1 returned to daily wetting 4 who had wet nightly continued on DDAVP for 3 more months by which time they were dry 1 had 1 wet night per fortnight and 1 had 1 wet night in 3 2 patients who were indifferent to wetting showed no response to desmopressin or placebo
Safety and adverse effects	None
Does the study answer the question?	The study showed that children treated with desmopressin had fewer wet nights at end of treatment compared to children treated with a placebo. (no usable data for meta-analysis)

Effect due to factor in study?	High and low dose desmopressin results grouped together.
Consistency of results with other studies?	Results similar to other studies of desmopressin.
Directly applicable to guideline population?	Children aged 4-12 years.
Internal Validity	Unclear allocation concealment and blinding

Ferrara P;Marrone G;Emmanuele V;Nicoletti A;Mastrangelo A;Tiberi E;Ruggiero A;Fasano A;Paolini P;

Homotoxicological remedies versus desmopressin versus placebo in the treatment of enuresis: a randomised, double-blind, controlled trial.

Ref ID 19 2008

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	151 patients were randomised: n=51 to desmopressin, n=50 to homotoxicological remedies and n=51 to receive placebo.
Inclusion/Exclusion Criteria	Exclusion criteria: NE associated with day-time symptoms (urgency, frequency, UI, urinary tract anomalies or infections)
Patient Characteristics	All patients had an ICCS definition of NE and none had received treatment for NE or homotoxicological remedies within the previous 3 months. Patients were aged 6 years to 14 years (mean 8.5 years).
Recruitment	From a Department of Paediatrics in Italy.
Setting	University Hospital.
Interventions/ Test/ Factor being investigated	Desmopressin vs. homotoxicological remedies vs. placebo
Comparisons	Between Desmopressin and homotoxicological remedies and placebo.
Length of Study/ Follow-up	Up to 3 months.
Outcome measures studied	Mean number of wet nights per week during the 3 months observation period and after 3 months of treatment. Number and percentage of non-responders, partial responders and full responders. Children relapsing, attaining 14 dry nights and adverse effects.
Results	151 patients were randomised. n=51 to desmopressin, n=50 to homotoxicological remedies and n=51 to receive placebo. Each patient was asked about a familiy history of bladder dysfunction and the number of wet nights per week. Urine analysis, urine culture and ultrasonography of kidney and bladder was conducted. A bladder diary that was completed by the patients or the parents was also used. The first group received desmopressin tablets 0.2mg, once in the evening, plus placebo drops, 20 drops three times a day and the third group received placebo tablets, once in the evening plus placebo drops, 20 drops three times a day. The treatment was started at different times for each patient, and each one was treated for 3 months. Non-responders to the therapy after the first 3 months period were withdrawn from the study. Children were classified as: -non- responders if there was no decrease, or less than 50% decrease in the number of wet nights compared to basline.

-partial responders if there was a 50% or more, but less than 90% decrease in the number of wet nights compared to baseline.
-Full responders if there was a 90% or more decrease in the number of wet nights compared to baseline.

The mean number of wet nights per week after the 3 months observation period was at least 6 or 7 in all groups.

The desmopressin group showed a statistically significant decrease (62.9%) in the number of wet nights compared to placebo (2.4%) ($p<0.001$). After 3 months, a full response was achieved in 26 out of 50 (52%) of the children treated with desmopressin compared with 0 out of 50 (0%) of the placebo group ($p<0.001$).

No relapse percentages were assessed between the desmopressin and placebo groups.

A statistically significant difference was reported. 26 out of 50 children treated with desmopressin achieved 14 consecutive dry nights and 0 out of 50 children treated with placebo ($p<0.001$).

Desmopressin group- 32 entered phase 2 (2 weeks wash out) and 18 did not re-enroll due to lack of response to the therapy.
Placebo group- None entered phase 2.

Safety and adverse effects No adverse effects were reported.

Does the study answer the question? Desmopressin is more effective than homotoxicological remedies and placebo. Homotoxicological remedies are more effective than placebo.

Effect due to factor in study? Yes.

Consistency of results with other studies? No other similar studies.

Directly applicable to guideline population? Patients were aged 6 years to 14 years.

Internal Validity Unclear allocation concealment and blinding

Lee T;Suh HJ;Lee HJ;Lee JE;

Comparison of effects of treatment of primary nocturnal enuresis with oxybutynin plus desmopressin, desmopressin alone or imipramine alone: a randomized controlled clinical trial

Ref ID 74 2005

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant #Deleted

Inclusion/Exclusion Criteria #Deleted

Patient Characteristics #Deleted

Recruitment Not reported

Setting 2 hospitals, between 2003 and 2004

Interventions/ Test/ Factor being investigated
Group A: 0.1 or 0.2 md desmopressin and 5 mg oxybutinin
Group B: 0.2 mg desmopressin (increased to 0.4 mg if no response)
Group C: 25 mg imipramine

Comparisons	Between treatment groups
Length of Study/ Follow-up	none
Outcome measures studied	0-1 wet nights a month, drop out, mean numebr of wet nights, continued response
Results	#Error
Safety and adverse effects	None reported
Does the study answer the question?	
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Age range of 5 to 15 years
Internal Validity	Unclear allocation concealment and blinding

Lottmann H;Froeling F;Alloussi S;El-Radhi AS;Rittig S;Riis A;Persson BE;

A randomised comparison of oral desmopressin lyophilisate (MELT) and tablet formulations in children and adolescents with primary nocturnal enuresis

Ref ID 35 2007

Study Type Randomised Controlled Trial **Funding** Ferring pharmaceutical

Number of participant	221 in total.
Inclusion/Exclusion Criteria	Inclusion: aged 5-15 years,and primary NE. Exclusion: daytime urgency, frequency (>7 micturitions during day time), voiding postponement, infrequency (< 3 voiding during daytime), the use of non-pharmacological treatment for NE in previous 60 days, organic urological disease, day time wetting, diabetes insipidus, UTI, clinically significant renal, hepatic, gastrointestinal, pulmonary, cardiovascular, endocrine, or neurological disease.
Patient Characteristics	The mean age was 9.6 (SD 2.4) years. 71.6% were male. 34.4% were aged 5-8 years, 40.8% were aged 9-11 years and 24.8% were aged 12-15 years.
Recruitment	Not reported.
Setting	26 centres in Europe
Interventions/ Test/ Factor being investigated	120 or 240 micrograms desmopressin melt.
Comparisons	0.2 or 2X0.2 mg desmopressin tablet.
Length of Study/ Follow-up	3 weeks
Outcome measures studied	Mean number of wet nights, and side effects.

Results	26 centres in France, Germany, the Netherlands, UK, Sweden, Denmark, Norway, Finland and Iceland 3 weeks of each treatment Mean number of wet nights per week The mean number of wet ngihts for the tablet was 1.88 (SD 1.94), and the mean number of wet nights for the melt was 1.90 (SD 1.85). The study reported that the treatment difference was -0.05 episodes/week (95% CI -0.21 to 0.1, p=0.5). The study reported that the age effect was -0.13 episodes/week per year age increased (95% CI -0.23 to -0.04) The study reported that the dose effect was 1.03 episodes/week for the high v. low dose (95% CI 0.53 to 1.53) Adverse events: 6 out of 109 patients in the melt desmopressin group had headaches compared to 0 out of 109 in the tablet desmopressin group. 3 out of 109 patients in the melt desmopressin group had diarrhoa compared to 0 out of 109 in the tablet desmopressin group. 3 out of 109 patients in the melt desmopressin group had viral gastroenteritis compared to 0 out of 109 in the tablet desmopressin group.
Safety and adverse effects	6 out of 109 patients in the melt desmopressin group had headaches compared to 0 out of 109 in the tablet desmopressin group. 3 out of 109 patients in the melt desmopressin group had diarrhoa compared to 0 out of 109 in the tablet desmopressin group. 3 out of 109 patients in the melt desmopressin group had viral gastroenteritis compared to 0 out of 109 in the tablet desmopressin group.
Does the study answer the question?	The study reported no signfiicant difference between tablet or melt form of desmopressin.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Age range 5-15 years.
Internal Validity	Unclear allocation concealment, no blinding

Muller D;Florkowski H;Chavez-Kattau K;Carlsson G;Eggert P;

The effect of desmopressin on short-term memory in children with primary nocturnal enuresis

Ref ID 175 2001

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	40 in total: 19 in group A (desmopressin), and 21 in group B (placebo).
Inclusion/Exclusion Criteria	Inclusion: at least 3 wet nights per week, and primary NE. Exclusion: organic causes of NE, anatomical abnormalities, or abnormal serum or urine analysis.
Patient Characteristics	29 out of 40 were boys. None had tried previous treatment. Mean baseline wetting per week was 5.35 (median 5.5 95% CI 4.5-6). The mean age in group A was 8.7, the median was 8.9 (Range 6-13). The mean age in group B was 8.6, median 8, and range 6.3-11.9.
Recruitment	Recruited from Children's Hospital, University of Kiel, Germany.

Setting	Germany.
Interventions/ Test/ Factor being investigated	Group A: 20 micro grams intransal desmopressin first Group B: 0.9% saline (Placebo) first
Comparisons	2 weeks of each treatment, then cross over
Length of Study/ Follow-up	4 weeks
Outcome measures studied	Mean number of wet nights during trial, and responders.
Results	2 weeks of each treatment Mean number of wet nights during trial: In group A the mean number of wet nights was 3.27, median 3, 95% CI 2 to 4. In group B the mean number of wet nights was 4.9, median 5.25, 95% CI 4.5-6. The difference between the two groups was highly significant (P<0.001) Responders 27 out of 40 children responded, no results for placebo There was no difference in reaction time between groups More children slept more deeply on desmopressin 14 out of 18 than on placebo (4 out of 18). P=0.03
Safety and adverse effects	Not reported
Does the study answer the question?	Study showed that more children responded when given desmopressin and had fewer wet nights compared to placebo treatment.
Effect due to factor in study?	Uncertain. The poor methodology (no allocation concealment, no blinding) and the absence on information on drop outs make it unclear whether the study was valid and had enough statistical power to detect any difference if it existed.
Consistency of results with other studies?	Consistent.
Directly applicable to guideline population?	Age 6-13 years
Internal Validity	Unclear allocation concealment and blinding

Rushton HG;Belman AB;Zaontz M;Skoog SJ;Sihelnik S;

Response to desmopressin as a function of urine osmolality in the treatment of monosymptomatic nocturnal enuresis: a double-blind prospective study

Ref ID 328 1995

Study Type	Randomised Controlled Trial	**Funding**	Rhone-Poulenc Rorer Pharmaceuticals Inc, Collegeville Pennsylvania

Number of participant	96 in total: 49 in Group A and 47 in Group B.
Inclusion/Exclusion Criteria	Inclusion: confirmed monosymptomatic NE, wet at least 6 nights during 2 week baseline period. Exclusion: organic causes of NE, day time wetting, organic urological disease, central diabetes insipidus, UTI in previous 18 months, use of drug which could affect urine concentration, medical treatment for hyperactivity or attention deficit disorder, history of acute or perennial rhinitis, rhinorrhoea or nasal polyps, clinically significant medical disease which would interfere with study.

Patient Characteristics	71 out of 91 were boys. The mean age was 9.7 years (range 7-14 years). Mean number of wet nights during 2 week baseline for group A was 11.16 (SD 2.44) and for group B was 10.96 (SD 2.53). In group A 36.7% had a positive family history of NE and in group B 29.8% did. There was no significant difference between the baseline characteristics of the two groups
Recruitment	Not reported
Setting	USA
Interventions/ Test/ Factor being investigated	Group A: 20 micro grams desmopressin spray (doubled if not completely dry after 14 nights) Group B: placebo (doubled if not completely dry after 14 nights)
Comparisons	Between treatment groups
Length of Study/ Follow-up	5 months
Outcome measures studied	Mean number of wet nights during first and last 2 weeks. Patient response during the 14 day observation period; excellent (2 or fewer wet nights), good (more than 2 wet nights but > 50% reduction in the number of wet nights), poor (<50% reduction wet n
Results	Group A were treated with 20 micro grams desmopressin, if children were not completely dry after 14 day the dose was doubled to 40 micro grams desmopressin Treatment for 4 weeks Mean number of wet nights during first 2 weeks: In Group A (20 micro grams desmopressin) the mean number of wet nights was 7.91 (SD 4.74) and in Group B (placebo) was 9.79 (SD 3.28). Mean number of wet nights during last 2 weeks: In Group A (40 micro grams desmopressin) the mean number of wet nights was 7.54 (SD 5.04) and in Group B (placebo) the mean number of wet nights was 9.79 (SD 3.63). Response rate In Group A (desmopressin) 10 out of 49 patients had an excellent response rate compared to 1 out of 47 in Group B (placebo). The study reported no differnece between responders and non responders by demographic variables (age, sex, race and family history).
Safety and adverse effects	Not reported.
Does the study answer the question?	The study showed that there was a higher response rate with desmopressin than with placebo. It also showed that children treated with desmopressin had fewer wet nights than those treated with placebo.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	Age range 7-14 years.
Internal Validity	Unclear allocation concealment and blinding

Uygur MC;Ozgu IH;Ozen H;Ozen S;Toklu C;Ergen A;Tekgul S;Remzi D;

Long-term treatment of nocturnal enuresis with desmopressin intranasal spray

Ref ID 283 1997

Study Type	Randomised Controlled Trial	**Funding**	Ferring Pharmaceutical, Sweden provided desmopressin

Number of participant	65 children in crossover trial. 11 excluded before RCT because did not respond to trial of desmopression. Total =54 children.
Inclusion/Exclusion Criteria	Inclusion: primary nocturnal enuresis. Exclusion: organic causes of NE, urological disease, non-response to 2 week trial of desmopressin.
Patient Characteristics	Age 7-17 years. Baseline wetting '3 or more wet nights/week'.
Recruitment	Not reported.
Setting	Turkey
Interventions/ Test/ Factor being investigated	Period A (54): desmopressin spray, 20mg or 40 mg if no response. Period B (54): placebo spray.
Comparisons	Desmopression compared to placebo.
Length of Study/ Follow-up	6 months.
Outcome measures studied	Number of wet nights in 2 weeks. Drop outs.
Results	Wet nights in 2 weeks: A=1; B=9.6 (no SDs). Drop out: 4 dropped out in total, 1 due to UTI 3 due to no response to desmopressin
Safety and adverse effects	None reported
Does the study answer the question?	The study showed that more children were dry when treated with desmopressin 20 mg or 40 mg than with desmopressin.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies with same comparison.
Directly applicable to guideline population?	Age range 7-17 years.
Internal Validity	Unclear allocation concealment and blinding

Vertucci P;Lanzi C;Capece G;Fano M;Gallai V;Margari L;Mazzotta G;Menegati E;Ottaviano S;Perini A;Perniola T;Roccella M;Tiberti A;Vecchio A;Biraghi M;

Desmopressin and imipramine in the management of nocturnal enuresis: a multicentre study

Ref ID 297 1997

Study Type	Randomised Controlled Trial	**Funding**	Not reported

Number of participant	57 in total: 29 who received desmorpessin then imipramine, and 28 who received imipramine then desmopressin.

Inclusion/Exclusion Criteria	Inclusion: primary NE aged over 5 years, wet at least 3 nights a week, and parental consent. Exclusion: organic or neurological dysfunction of the urinary system.
Patient Characteristics	The age range was 6 to 15 years. The mean age was 10 years. 37 out of 57 were male.
Recruitment	Children at Child Neuropsychiatry clinics in Italy.
Setting	Child Neuropsychiatry Clinics Italy.
Interventions/ Test/ Factor being investigated	Group A: Desmopressin 30 mcg intranasal then imipramine 0.9 mg/kg. Group B: Imipramine 0.9 mg/kg then desmopressin 30 mcg intranasal.
Comparisons	Between desmopresisn and imipramine.
Length of Study/ Follow-up	2 weeks
Outcome measures studied	Number of wet nights, number achieving 14 consecutive dry nights, drop outs, and side effects.
Results	Data was presented in graphs - data presented below was from Cochrane review Treatment was for 3 weeks of each. Results shown are for after the first 3 weeks of treatment (patients had only received one drug) Mean number of wet nights during first arm of trial In group A (desmopressin) the mean number of wet nights was 1, in group B (imipramine) the mean number of wet nights was 2.8. Number who achieved 14 consecutive dry nights: 25 out of 29 achieved 14 consecutive dry nights when treated with desmopressin compared to 19 out of 28 who were treated with imipramine. Drop outs: 5 in total. Side effects: Desmopressin: 1 had back pain and 1 had a an inflamed nasal mucosa. Imipramine: 1 had pallor and restlessness and cold extremities.
Safety and adverse effects	Desmopressin: 1 had back pain and 1 had an inflamed nasal mucosa. Imipramine: 1 had pallor, restlessness and cold extremities.
Does the study answer the question?	Study compared desmorpessin to imipramine to show that both reduced the number of wet nights, however desmopressin was more effective than imipramine.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged 6 to 15 years.
Internal Validity	Unclear allocation concealment and blinding

Wille S;

Comparison of desmopressin and enuresis alarm for nocturnal enuresis

Ref ID 127 1986

Study Type	Randomised Controlled Trial	**Funding**	Not reported.

Number of participant	50 patients recruited, 25 allocated to each arm. Only 46 patients completed the trial, 22 of which were treated with the enuresis alarm, 24 were treated with intranasal desmopressin
Inclusion/Exclusion Criteria	Inclusion: older than 6 years, not dry for more than 6 months since 3 years, wet at least 3 times a week, and written informed consent. Exclusion: treatment for NE in previous years, day time wetting, cardiovascular disease, renal disorder, neurological disorder, or chronic UTI.
Patient Characteristics	Group A had a mean number of wet nights at baseline line of 2.1 Group B had a mean number of wet nights at baseline line of 1.9
Recruitment	Patients referred to S. Wille's clinic.
Setting	Sweden, treatment at home.
Interventions/ Test/ Factor being investigated	Group A: intranasal desmopressin Group B: alarm
Comparisons	Between groups A and B
Length of Study/ Follow-up	3 months
Outcome measures studied	Number of children dry for 14 consecutive nights, and relapse.
Results	Success of being for 28 days with only 5 wet nights or achieving a lower wetting score (score: very wet = 3, a little wet = 2, dry = 1): In group A (desmopressin) 17 out of 24 children became dry compared to 19 out of 22 in group A (alarm). The study stated that at the end of treatment both groups were significantly drier than before the treatment however the alarm group was more successful (alarm $p<0.001$; desmopressin $p<0.02$). There was no significant difference between group A (desmopressin) and group B (alarm). Group A (desmopressin) had significantly more dry nights than group B (alarm) in the first 3 weeks ($p<0.001$). However during the last 9 weeks of treatment the alarm group had more dry nights, and significantly more in the 11th week ($p<0.002$). The study stated that due to the high relapse rate in the desmopressin group, over all during the first 2 weeks of treatment and at 3 month follow up the alarm group was significantly better than the desmopressin group ($p<0.02$, $p<0.001$, 2 weeks and 3 months respectively). Relapse: 1 patient in the alarm group relapsed in the 3 month follow up compared to 10 in the desmopressin group. Drop out: 1 child from the alarm group dropped out due to lack of improvement. Adverse events: In the alarm group 78% had false alarms, 19% said the alarm did not work when the child was wet, 56% said the alarm did not wake the child, 56% said the alarm woke other family members instead and 1 patient was afraid of the alarm. In the desmopressin group 13% reported nasal discomfort, 3% had occasional nose bleeds and 5% experienced a bad taste in the throat. The study included a cross over of treatments for children who were unsuccessful in their original treatment group. Of the children who changed from desmopressin to alarm 2 children improved by a 2 month follow up, 3 were better than before and 5 did not respond. Of the children who changed from alarm to desmopressin 2 children did improve but subsequently relapsed. There was no significant difference between the cross over results.

Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that both alarm treatment and desmopressin lead to a significant reduction in the number of wet nights. The study showed that alarm treatment was more successful in achieving 28 dry nights (with less than 5 wet nights) than desmopressin, however this difference was not significant until the high relapse rate of desmopressin was taken into account. With alarms then being significantly more effective. The desmopressin group had a higher relapse rate than the alarm group. More patients receiving alarm therapy reported side effects than those receiving desmopressin.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies comparing desmopressin and alarm.
Directly applicable to guideline population?	Patients were aged over 6 years.
Internal Validity	Unclear allocation concealment and blinding

Grading: 2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

Del G;Del G;Cennamo M;Auriemma R;Del G;Verni M;

Desmopressin is a safe drug for the treatment of enuresis

Ref ID 247 2005

Study Type Cohort **Funding** Not reported

Number of participant	541 patients
Inclusion/Exclusion Criteria	Inclusion: aged over 5 years, absence of malformations and infections of the urinary tract, absence of psychological disorders or neurological alterations, number of wet nights greater than 5 to 7.
Patient Characteristics	Children were aged over 5 years.
Recruitment	Selected patients monitored for 2 years (no details).
Setting	Italy
Interventions/ Test/ Factor being investigated	30 to 40 micrograms intranasal desmopressin.
Comparisons	0.3 to 0.4 mg tablet desmopressin
Length of Study/ Follow-up	3 months.
Outcome measures studied	Side effects.
Results	3 months of treatment Children treated with intranasal desmopressin 7 out of 153 patients had weight gain during the first 4 days of therapy, 1 out of 153 had vomiting and abdominal pain and 1 out of 153 had headache and abdominal pain. Children treated with tablet desmopressin 22 out of 388 patients had side effects such as headache, vomiting, stomach ache, lack of appetite, vesical tenesmus, diarrhea, epistaxis, dizziness, drowsiness and weight gain in 3 patients; 10 patients interrupted treatment due to weight gain.
Safety and adverse effects	Children treated with intranasal desmopressin 7 out of 153 patients had weight gain during the first 4 days of therapy, 1 out of 153 had vomiting and abdominal pain and 1 out of 153 had headache and abdominal pain. Children treated with tablet desmopressin 22 out of 388 patients had side effects such as headache, vomiting, stomach ache, lack of appetite, vesical tenesmus, diarrhea, epistaxis, dizziness, drowsiness and weight gain in 3 patients; 10 patients interrupted treatment due to weight gain.
Does the study answer the question?	The study showed some children treated with intranasal desmopressin had weight gain, vomiting abdominal pain and headache. The study showed some children treated with tablet desmopressin had headache, vomiting, stomach ache, lack of appetite, vesical tenesmus, diarrhea, epistaxis, dizziness, drowsiness and weight gain.
Effect due to factor in study?	Yes

Consistency of results with other studies?	
Directly applicable to guideline population?	Children were aged over 5 years.
Internal Validity	Adequately addressed

Hjalmas K;Hanson E;Hellstrom AL;Kruse S;Sillen U;

Long-term treatment with desmopressin in children with primary monosymptomatic nocturnal enuresis: an open multicentre study. Swedish Enuresis Trial (SWEET) Group

Ref ID 739 1998

Study Type Cohort **Funding** Not reported

Number of participant	393 patients
Inclusion/Exclusion Criteria	Inclusion: Aged 6 to 12 years and monosymptomatic nocturnal enuresis. Exclusion: day incontinence, or previous urological history such as UTI.
Patient Characteristics	Children had an age range of 6 to 12 years.
Recruitment	Recruited to multi centre trial (no details).
Setting	Multi centre trial, Sweden.
Interventions/ Test/ Factor being investigated	20 to 40 micrograms intranasal desmopressin .
Comparisons	No comparison.
Length of Study/ Follow-up	Not reported
Outcome measures studied	Side effects.
Results	28 days of treatment or long term (unspecified) treatment. The study showed 2.5% of 393 children reported mild adverse events of nasal irritation and abdominal pain on short term desmopressin and 2% of 242 children had temporary bouts of aggression when on long term desmopressin.
Safety and adverse effects	2.5% of children reported mild adverse events of nasal irritation and abdominal pain on short term desmopressin and 2% had temporary bouts of aggression when on long term desmopressin.
Does the study answer the question?	The study showed 2.5% of children reported mild adverse events of nasal irritation and abdominal pain on short term desmopressin and 2% had temporary bouts of aggression when on long term desmopressin.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	
Directly applicable to guideline population?	Age range 6 to 12 years.
Internal Validity	Adequately addressed

Tullus K;Bergstrom R;Fosdal I;Winnergard I;Hjalmas K;

Efficacy and safety during long-term treatment of primary monosymptomatic nocturnal enuresis with desmopressin. Swedish Enuresis Trial Group

Ref ID 703 1999

Study Type	Cohort	**Funding**	Ferring Pharmaceuticals, Malmo, Sweden.

Number of participant	245 patients
Inclusion/Exclusion Criteria	Inclusion: primary monosymptomatic NE, aged 6 to 12 years, no evidence of organic urinary tract pathology, and no history of diurnal symptoms. Exclusion: clinically significant illness affecting any of the other major organ systems.
Patient Characteristics	Children were aged 6 to 12 years.
Recruitment	Consecutive patients at 24 centres.
Setting	Hospital and district paediatric clinics, Sweden.
Interventions/ Test/ Factor being investigated	Intranasal desmopressin.
Comparisons	No comparison.
Length of Study/ Follow-up	4 weeks observation period, a six weeks dose titration period and a year long term treatment period.
Outcome measures studied	Side effects
Results	12 months of treatment. The study showed 16% of children had headaches and 13% had gastroenteritis. 20% had psychological disturbances which included 4% with nervousness, 4% with aggressive reactions and 2% with nightmares. 1% dropped out due to abdominal pain, 1% due to aggressive reactions, 0.5% due to nightmares and 0.25% due to loss of appetite.
Safety and adverse effects	The study showed 16% of children had headaches and 13% had gastroenteritis. 20% had psychological disturbances which included 4% with nervousness, 4% with aggressive reactions and 2% with nightmares. 1% dropped out due to abdominal pain, 1% due to aggressive reactions, 0.5% due to nightmares and 0.25% due to loss of appetite.
Does the study answer the question?	The study showed some children treated with intranasal desmopressin had headaches, gastroenteritis, psychological disturbances, abdominal pain, aggressive reactions, nightmares and loss of appetite.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	Children were aged 6 to 12 years.
Internal Validity	Adequately addressed

Wolfish NM;Barkin J;Gorodzinsky F;Schwarz R;

The Canadian Enuresis Study and Evaluation--short- and long-term safety and efficacy of an oral desmopressin preparation

Ref ID 4089 2003

Study Type	Cohort	**Funding**	Not reported

Number of participant	256 patients
Inclusion/Exclusion Criteria	Inclusion: good health, no organic systemic pathology, and wet at least 10 out of 28 consecutive nights.
Patient Characteristics	Mean age 9.6 years and age range of 6 to 18 years. 79.3% were male and 80% had tried previous treatment (alarm or drugs).
Recruitment	Not reported.
Setting	Canada.
Interventions/ Test/ Factor being investigated	0.2 to 0.4 mg tablet desmopressin
Comparisons	No comparison.
Length of Study/ Follow-up	No follow up
Outcome measures studied	Side effects.
Results	1 month of treatment The study showed out of 256 patients, 2 children withdrew from the trial 1 due to abdominal pain and 1 due to headache and abdominal pain
Safety and adverse effects	2 out of 256 children withdrew from the trial, 1 due to abdominal pain and 1 due to headache and abdominal pain.
Does the study answer the question?	The study showed out of 256 patients, 2 children withdrew from the trial 1 due to abdominal pain and 1 due to headache and abdominal pain.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	Age range of 6 to 18 years.
Internal Validity	Adequately addressed

Grading: 2-	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

Figueroa TE;Benaim E;Griggs ST;Hvizdala EV;

Enuresis in sickle cell disease

Ref ID 3004 1987

Study Type	Cohort	**Funding**	Not reported.

Number of participant	10 patients
Inclusion/Exclusion Criteria	Inclusion: sickle cell disease and primary enuresis.
Patient Characteristics	Age range 6 to 12 years.
Recruitment	Patients at centre.
Setting	Regional sickle cell center, USA.
Interventions/ Test/ Factor being investigated	Intranasal desmopressin.
Comparisons	No comparison.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Side effects.
Results	6 months of treatment The study showed 4 children did not respond to intranasal desmopressin and one of these children stopped using intranasal desmopressin due to headaches.
Safety and adverse effects	1 out of 10 children with sickle cell disease stopped using intranasal desmopressin due to headaches.
Does the study answer the question?	The study showed only 1 out of 10 children with sickle cell disease stopped using intranasal desmopressin due to headaches.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other studies.
Directly applicable to guideline population?	Children had sickle cell disease, and their age range was 6 to 12 years.
Internal Validity	Adequately addressed

Robson WLM;Leung AKC;

Side effects associated with DDAVP treatment of nocturnal enuresis

Ref ID 3046 1994

Study Type	Cohort	**Funding**	Not reported

Number of participant	77 patients
Inclusion/Exclusion Criteria	Inclusion: patients seen in clinics and treated with desmopressin
Patient Characteristics	Mean age 9.4 years and age range 5.3 to 15.3 years. 70% were male and 64% were responders. 60% had 10 micrograms desmopressin, and 40% had 20 micrograms or higher desmopressin.
Recruitment	Patients seen from November 1989 to March 1993 and treated with desmopressin.
Setting	Pediatric nephrology clinic,Canada.
Interventions/ Test/ Factor being investigated	10 to 40 micrograms intranasal desmopressin.
Comparisons	No comparison.
Length of Study/ Follow-up	Not reported.
Outcome measures studied	Side effects.
Results	4 weeks of treatment. The study showed 1 out of 77 children suffered from headaches and 1 out of 77 children had emotional lability.
Safety and adverse effects	The study showed 1 out of 77 children suffered from headaches and 1 out of 77 children had emotional lability.
Does the study answer the question?	The study showed 1 out of 77 children suffered from headaches and 1 out of 77 children had emotional lability.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	Mean age 9.4 years.
Internal Validity	Adequately addressed

Question: What is the clinical and cost effectiveness of tricyclic drugs for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Burke JR;Mizusawa Y;Chan A;Webb KL;

A comparison of amitriptyline, vasopressin and amitriptyline with vasopressin in nocturnal enuresis.

Ref ID 325 1995

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	45 in total, 14 in group A (amitriptyline), 17 in group B (desmopressin), 14 in group C (desmopressin and amitriptyline)
Inclusion/Exclusion Criteria	Inclusion: 6-17 years, at least 3 wet nights a week for proceeding 3 month period, not dry for more than 6 months Exclusion: organic causes of NE, enuresis treatment in previous 6 months, neurogenic disorder, UTI, abnormal urinalysis haemotology or blood biochemistry, concomitant medication known to interfer with study medication
Patient Characteristics	In group A the mean age was 8.6 (SD 2.4) years, the mean baseline wetting was 5.8 (SD 0.9) In group B the mean age was 8.9 (SD 2.5) years, the mean baseline wetting was 6.0 (SD 0.9) In group C the mean age was 8.9 (SD 2.4) year, the mean baseline wetting was 6.3 (SD 0.9)
Recruitment	Not reported
Setting	Australia
Interventions/ Test/ Factor being investigated	Group A: amitriptyline hydrocholoride (25 mg or 50mg) Group B: intranasal desmopressin (20 micro grams) Group C: desmopressin and amitriptyline
Comparisons	Between treatment groups
Length of Study/ Follow-up	12 weeks
Outcome measures studied	Number of children cured, drop outs, mean number of wet nights at end of treatment and follow up
Results	16 weeks of treatment Number of children cured: In group A (amitriptyline) 3 out of 14 became dryt, compared to in group B (desmopresisn) 1 out of 17 and in group C (desmopresisn and amitriptyline) 4 out of 14 Number of drop outs: In group A (amitriptyline) 0 out of 14 dropped out, in group B (desmopresisn) 3 out of 17 dropped out, in group C (desmopresisn and amitriptyline) 3 out of 14 dropped out Mean number of wet nights per week at end of treatment: The mean number of wet nights per week for group A (amitriptyline) was 3.3 (SD 1.9), for group B (desmopresisn) was 4.7 (SD 1.7) and for group C (desmopressin and amitriptyline) was 3.3 (SD 2.5) Mean number of wet nights per week at 12 week follow up: The mean number of wet nights per week for group A (amitriptyline) was 3.9 (SD 2.9), for group B (desmopresisn) was 3.8 (SD 1.9) and for group C (desmopressin and amitriptyline) was 5.1 (SD 3.2)
Safety and adverse effects	None reported

Does the study answer the question?	The study showed that more children became dry when treated with amitriptyline and desmopressin, patients treated with amitriptyline alone and with desmopressin had fewer wet nights during treatment but at follow up desmopressin alone or amitriptyline alone had the fewest number of wet nights
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Aged 6-17 years
Internal Validity	Trial was stopped early

Poussaint AF;Ditman KS;Greenfield R;

Amitriptyline in childhood enuresis

Ref ID 584 1966

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	50 in total (60 before drop outs) Trial 1: 16 in each group Trial 2: 9 in each group
Inclusion/Exclusion Criteria	Inclusion: wet at least 1 night a week. Exclusion: organic causes of NE, or learning difficulties.
Patient Characteristics	The age range was 5 to 15 years. 80% had never been dry since birth. The remainder had had brief periods of dryness.
Recruitment	Referred by doctor.
Setting	Department of psychiatry neuropsychiatric UCLA USA
Interventions/ Test/ Factor being investigated	Trial 1: Group A: amitriptyline (25 mg for children aged less than 12 years, 50 mg for children aged over 12 years Group B: placebo Trial 2: Group A: amitriptyline (25 mg for children aged less than 12 years, 50 mg for children aged over 12 years Group B: placebo
Comparisons	Between treatment groups.
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Number of wet nights, and side effects.
Results	Data taken from Cochrane review because graphical data only presented in paper. There were 10 drop outs in total Trial 1: Treatment for 4 weeks Mean number of wet nights in last week of treatment: In group A (amitriptyline) the mean number of wet nights was 3.1, while in group B (placebo) the mean number of wet nights was 4.6. Side effects: (same data as trial 2) Amitriptyline:

	7 reported being irritable, 2 were calmer, 10 nocturia, 3 drowsy, 2 headache, 1 lower appetite, 1 fatigue, 1 stomach ache, and 1 scleral injection. Placebo: 5 reported being irritable, 5 stomach ache, 1 fatigue, and 1 lower appetite. Trial 2: Treatment for 8 weeks Mean number of wet nights in last week of treatment: In group A (amitriptyline) the mean number of wet nights was 4.1, while in group B (placebo) the mean number of wet nights was 5.5. Side effects: (same data as trial 1) Amitriptyline: 7 reported being irritable, 2 were calmer, 10 nocturia, 3 drowsy, 2 headache, 1 lower appetite, 1 fatigue, 1 stomach ache, and 1 scleral injection. Placebo: 5 reported being irritable, 5 stomach ache, 1 fatigue, and 1 lower appetite.
Safety and adverse effects	Amitriptyline: 7 reported being irritable, 2 were calmer, 10 nocturia, 3 drowsy, 2 headache, 1 lower appetite, 1 fatigue, 1 stomach ache, 1 scleral injection Placebo: 5 reported being irritable, 5 stomach ache, 1 fatigues, 1 lower appetite
Does the study answer the question?	Both trials compared amitriptyline to placebo and showed amitriptyline is more effective than placebo
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged 5 to 15 years.
Internal Validity	Unclear allocation concealment

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Agarwala S;Heycock JB;

A controlled trial of imipramine ('Tofranil') in the treatment of childhood enuresis

Ref ID 571 1968

Study Type Randomised Controlled Trial **Funding** Not stated.

Number of participant	29 in total in this cross over trial.
Inclusion/Exclusion Criteria	Inclusion: parents consider the enuresis to be a problem, aged over 6 years, wet 6-7 times a week. Exclusion: organic causes of NE or mental retardation.
Patient Characteristics	15 out of 29 were boys and the age range was 6-12 years. Some had previously been treated with imipramine.
Recruitment	All currently attending the Outpatient Department with enuresis as their main complaint.
Setting	Sunderland Children's Hospital.
Interventions/ Test/ Factor being investigated	Group A: 25 mg imipramine for 2 weeks and dose doubled (50mg) for another 2 weeks if no response. Group B: placebo.
Comparisons	Between treatment groups.
Length of Study/ Follow-up	4 weeks.
Outcome measures studied	14 consecutive dry nights, mean number of wet nights in 2 weeks of treatment, and side effects.
Results	Treatment for 2 weeks or 4 if no response Number of children who achieved 14 consecutive dry nights: In Group A 2 out of 29 achieved 14 consecutive dry nights compared to 0 out of 29 in group B. Mean number of wet nights: Group A had a mean number of 5.5 (SD 3.3) wet nights in the 2 weeks of treatment compared to 7.8 (4) in group B Side effects: 1 patient in group A suffered dizziness when treated with 50mg imipramine.
Safety and adverse effects	1 patient in group A suffered dizziness when treated with 50mg imipramine.
Does the study answer the question?	Yes it helps answer the question regarding the clinal effectiveness of Imipramine (tricyclic drug) for nocturnal eneuresis. The author concludes that Imipramine is overall superior to placeo and did not occur by chance.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies comparing imiparmine to placebo.
Directly applicable to guideline population?	Yes
Internal Validity	Unclear allocation concealment

Attenburrow AA;Stanley TV;Holland RP;

Nocturnal enuresis: a study

Ref ID 464 1984

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	33 in total: 12 in viloxazine group, 9 in imipramine group, 12 in placebo
Inclusion/Exclusion Criteria	Inclusion: suitable for drug therapy, parental consent, no abnormalities in blood or urine. Exclusion: organic causes.
Patient Characteristics	11 out of 33 were boys, and the median age was 7 years (range 5 to 13 years). The baseline mean number of dry nights per week was 2.4 for imipramine group and 1.3 for placebo group. Most had received previous simple treatments (lifting and fluid restriction).
Recruitment	Those aged over 5 years presenting with nocturnal enuresis at the department of paediatrics.
Setting	The Royal Hospital for Sick Children, Glasgow.
Interventions/ Test/ Factor being investigated	Group A:50mg imipramine for children aged under 10 years, 75 mg imipramine for children aged over 10 years Group B: placebo Study also included a group treated with viloxamine, not included for this review.
Comparisons	Between treatment groups.
Length of Study/ Follow-up	2 weeks
Outcome measures studied	Number of dry nights. Side effects.
Results	Mean number of wet nights in the final week of treatment: group A (imipramine) had 3.2 (SD 4.5), group B (placebo) had 5.7 (2.4) Mean number of wet nights per week at follow up: Group A (imipramine) = 4.2 (4.8) compared to group B (placebo)= 5.7 (2.1). Side effects In group A 4 had lethargy, 3 had constipation, 2 had upset stomach, 1 had vomiting, sweating and sickness, 1 had vomiting and drowsiness leading to withdrawal, 1 had dizziness and dry mouth, and 1 had anorexia. In group B 2 had a rash and 1 had nightmares. Drop outs= 13 in total
Safety and adverse effects	In group A 4 had lethargy, 3 had constipation, 2 had upset stomach, 1 had vomiting, sweating and sickness, 1 had vomiting and drowsiness leading to withdrawal, 1 had dizziness and dry mouth, and 1 had anorexia. In group B 2 had a rash and 1 had nightmares.
Does the study answer the question?	Yes it looks at the clinical effectivenss of a tricyclic drug (imipramine) for nocturnal eneuresis.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies comparing imipramine to placebo.
Directly applicable to guideline population?	Children aged 5 to 13 years.

Internal Validity	Unclear allocation concealment

Batislam E;Nuhoglu B;Peskircioglu L;Emir L;Uygur C;Germiyanoglu C;Erol D;

A prostaglandin synthesis inhibitor, diclofenac sodium in the treatment of primary nocturnal enuresis

Ref ID 114 1995

Study Type	Randomised Controlled Trial	**Funding**	Not reported

Number of participant	78 in total 16 in imipramine group, 12 in placebo group
Inclusion/Exclusion Criteria	Inclusion: primary Ne, wet at least 3 nights a week Exclusion: orgainc causes, previous treatment
Patient Characteristics	48 out of 78 were male, age range 6 to 18 years
Recruitment	Not stated.
Setting	
Interventions/ Test/ Factor being investigated	Group A: imipraimne Group B: placebo Study also evaluated diclofenac and imipramine with diclofenac, not included for this review
Comparisons	between treatment groups
Length of Study/ Follow-up	3 months
Outcome measures studied	relapse at 3 months, 50% improvement, side effects, failure to improve ore relapse rate
Results	50% or greater improvement 2 out of 16 in the imipramine group and 6 out of 12 in placebo group Adverse events 8 had mild gastrointestinal
Safety and adverse effects	8 had mild gastrointestinal
Does the study answer the question?	Study comapred imipramine to placebo
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies comparing imipramine to placebo
Directly applicable to guideline population?	Yes age range 6 to 18 years
Internal Validity	Unclear allocation concealment and blinding

Danquah SA;

Comparative treatment of nocturnal enuresis among Ghanaian school children

Ref ID 364 1975

Study Type	Randomised Controlled Trial	**Funding**	None reported

Number of participant	30 boys, 10 in each treatment group (Group A amitriptyline, Group B alarm and Group C shaming)
Inclusion/Exclusion Criteria	Inclusion: boys with enuresis Exclusion: those who were undergoing tradional treatment
Patient Characteristics	The mean age was 10.4 years and the mean IQ was 85.4 (20.12 SD).
Recruitment	From a fishing village in Ghana.
Setting	Ghanian fishing community, at home
Interventions/ Test/ Factor being investigated	Group A: amitripyline Group B: alarm The study also looked at shaming which is not a relevent comparison so results are not reported
Comparisons	Between treatment groups.
Length of Study/ Follow-up	3 months
Outcome measures studied	Change in number of wet nights.
Results	7 weeks treatment The mean number of wet nights per week at the end of treatment was 3.2 for the alarm group and 4 for the amitripyline group. The median number of days for initial arrest were 15.5 for alarm therapy and 20 for amitriptyline. Follow-up was conducted after 3 months post treatment. Alarm therapy was the only treatment that was continuously successful. The post-treatment ranking (post treatment frequency of bed wetting) was 3.20 and following treatment was 1.49, t=3.98, p<0.001.
Safety and adverse effects	None reported
Does the study answer the question?	The alarm was found to be quicker and more effective.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	The study only included boys and the mean age was 10.4 years.
Internal Validity	Unclear allocation concealment and blinding

Drew LR;

Control of enuresis by imipramine

Ref ID 581 1966

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	28 in total; 9 were subjects for both parts. 17 children were subjects for the second part only, and 2 were subjects for the first part only.

Inclusion/Exclusion Criteria	Inclusion: wet at least 3 nights a week and age 5 to 15 years.
Patient Characteristics	The age range was 5 to 15 years. The baseline mean number of wet nights was 65.8% in group A (placebo then imipramine) and 64.7% in group B (imipramine then placebo).
Recruitment	From a childrens home in Melbourne.
Setting	Childrens home, Melbourne
Interventions/ Test/ Factor being investigated	Group A: Placebo then imipramine Group B: Imipramine then placebo Patients were given 2 tablets. If they had a wet night in the first week the dose was doubled to 4 tablets
Comparisons	Between imipramine and placebo.
Length of Study/ Follow-up	None.
Outcome measures studied	Number of wet nights and adverse events.
Results	4 weeks on each treatment. After these 4 weeks continued on imipramine or placebo. Number of wet nights: Group A (placebo then imipramine) had 3.79 wet nights per week, while group B (imipramine then placebo) had 2.38 wet nights per week. Adverse events: None
Safety and adverse effects	None
Does the study answer the question?	Imipramine is more effective than placebo
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies comparing imipramine and placebo
Directly applicable to guideline population?	Children were aged 5 to 15 years
Internal Validity	Unclear allocation concealment and blinding.

Esmaeili M;

Combined treatment with oxybutynin and imipramine in enuresis

Ref ID 636 2008

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	89 in total: 29 in imipramine group, 26 in oxybutinin group and 34 in imipramine and oxybutinin group.
Inclusion/Exclusion Criteria	Inclusion: primary NE, wet at least 2 nights a week for preceding 3 months, and never been dry for more than 6 months. Exclusion: voiding dysfunction other than primary NE, urologic and neurological abnormalities, prior pharmacological treatment, UTI, or diurnal enuresis.
Patient Characteristics	The mean age was 8.9 (SD 1.6) years, and age range 6-14 years. The mean baseline wetting was 5.1 (SD 1.1) days per week.

Recruitment	Patients were referred to the paediatric nephrology clinic at Mashhad University of Medical Sciences between November 2003 and March 2004.
Setting	Iran.
Interventions/ Test/ Factor being investigated	Group A: 10-25 mg imipramine Group B: 3.75-5 mg oxybutinin Group C: imipramine and oxybutinin
Comparisons	Between treatment groups.
Length of Study/ Follow-up	1 month.
Outcome measures studied	Number of children achieving 14 consecutive dry nights, and mean number of wet nights per week during treatment.
Results	1 month of treatment Number of children who achieved 14 consecutive dry nights: 4 out of 29 children in group A (imipramine) group were cured, compared to 6 out of 26 in group B (oxybutinin) and 14 out of 34 in group C (imipramine and oxybutinin). The mean number of wet nights per week during treatment: The mean number of wet nights per week during treatment was 3.5 (SD 2) for group A (imipramine), the mean for group B (oxybutinin) was 2.5 (SD 1.7) and for group C (imipramine and oxybutinin) the mean was 1.4 (SD 1.5).
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that the most effective treatment was imipramine combined with oxybutinin.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar with other study with same comparison.
Directly applicable to guideline population?	Age range 6-14 years.
Internal Validity	Unclear allocation concealment and blinding

Forsythe WI;Merrett JD;

A controlled trial of imipramine ('Tofranil') and nortriptyline ('Allegron') in the treatment of enuresis

Ref ID 561 1969

Study Type Randomised Controlled Trial **Funding** MESSRS GEIGY Ltd. And MESSERS DISTA Ltd

Number of participant	298 in total, 78 in imipramine and placebo group, 88 in nortriptyline and placebo group and 87 in placebo group
Inclusion/Exclusion Criteria	Inclusion: wet at least 6 nights a week Exclusion: UTI
Patient Characteristics	Age range of up to 15 years, 6 children aged under 5 years
Recruitment	Not reported
Setting	Royal Belfast Hospital for Sick Children

Interventions/ Test/ Factor being investigated	Imipramine and nortriptyline placebo Nortriptyline and imipramine placebo
Comparisons	Matching placebo
Length of Study/ Follow-up	8 weeks follow up
Outcome measures studied	14 consecutive dry nights, number of children who had a 50% reduction in the number of wet nights
Results	8 weeks of treatment The number of children who achieved 14 consecutive dry nights: 1 out of 76 children in the imipramine and placebo group achieved 14 consecutive dry nights compared to 1 out of 86 in the notriptyline and placebo group and 1 out of 85 in the placebo group The number of children who had a 50% reduction in the number of wet nights: 22 out of 76 children in the imipramine and placebo group achieved 14 consecutive dry nights compared to 34 out of 86 in the notriptyline and placebo group and 21 out of 85 in the placebo group
Safety and adverse effects	None reoprted
Does the study answer the question?	Treatment with imipramine or nortirptyline is significantly more effective than placebo treatment
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Age range of up to 15 years, 6 children aged under 5 years
Internal Validity	Unclear allocation concealment and blinding

Fournier JP;Garfinkel BD;Bond A;Beauchesne H;Shapiro SK;

Pharmacological and behavioral management of enuresis

Ref ID 346 1987

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	64 in total59 completed the study 7 in imipramine, 7 in alarm, 7 in alarm and placebo, 8 in imipramine and alarm, 8 in random awakening, 8 in random awakeing and placebo, 8 in imipramine and random awakening and 6 in placebo.
Inclusion/Exclusion Criteria	Inclusion: aged between 5 and 14 years, no history of UTI or disease, no physical or neurological disorder, at least 2 wet nights a week for previous 6 months, no treatment in previous 3 months, no significant cognitive impairment or mental retardation, imformed consent to random allocation of treatment
Patient Characteristics	73% were boys, the mean age was 8.5 years, 70% of children lived with their biological parent, 14% lived with a single parent, 83% were either the oldest or second eldest child in their family, 77% had had a first degree relative with enuresis and 61% had another relative with enuresis
Recruitment	Newspaper adverts and referred from paediatricians
Setting	at home

Interventions/ Test/ Factor being investigated	Group A: imipramine Group B: alarm Group C: placebo Group D: alarm with imipramine Group E: alarm with placebo The study also considered random waking, placebo with random waking and imiprmaine with random waking which are not relevant comparators for this reivew and were not included
Comparisons	Between treatment groups
Length of Study/ Follow-up	3 months
Outcome measures studied	Mean number of wet nights per week at the end of treatment
Results	Treatment for 6 weeks At the end of treatment the imipramine group had a mean of 1 wet night per week; the alarm group had 2.5 wet nights per week; the placebo group had 5 wet nights per week; the imiprmaine with alarm group had 1 wet nights per week; there were no results for the alarm and placebo group Drop out: In total 4 boys dropped out due to side-effects or non-compliance and 1 girl dropped out due to having a UTI
Safety and adverse effects	None reported
Does the study answer the question?	The study showed that imipramine had a fasted effect than the other treatments, however at 4 weeks the most effective treatments were alarm, alarm with imipramine and imipramine alone. At the 3 month follow up the most sucessful treatments were alarm, imipramine and alarm with placebo.
Effect due to factor in study?	Yes (NB there is a 15% spontaneous cure rate)
Consistency of results with other studies?	Similar to other studies with same comparison
Directly applicable to guideline population?	children were aged 5 - 14 years old
Internal Validity	Unclear allocation concealment and blinding

Hagglund TB;Pakkulainen K.V.;

Enuretic children treated with imipramine (Tofranil): a cystometric study

Ref ID 1742 1964

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	34 in study, 18 children in the treatment group, 16 in control.
Inclusion/Exclusion Criteria	Inclusion: Normal IQ and wet every night. Exclusion: UTI, other urological abnormality, abnormal EEG, and daytime wetting.
Patient Characteristics	Age range of 4 to 14 years. 27 boys and 7 girls.
Recruitment	Not reported.
Setting	Finland.

Interventions/ Test/ Factor being investigated	Imipramine
Comparisons	Placebo
Length of Study/ Follow-up	3 to 8 months
Outcome measures studied	Number of children who achieved 14 consecutive dry nights
Results	The number of children who achieved 14 consecutive dry nights: 3 out of 7 children in the imipramine group achieved 14 consecutive dry nights compared to 0 out of 8 in the placebo group.
Safety and adverse effects	None reported.
Does the study answer the question?	Imipramine is more effective than placebo.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Age range of 4 to 14 years.
Internal Validity	Unclear allocation concealment and blinding.

Harrison JS;Albino VJ;

An investigation into the effects of imipramine hydrochloride on the incidence of enuresis in institutionalized children

Ref ID 551 1970

Study Type Randomised Controlled Trial **Funding** Giegy pharmaceutical provided the imipramine and placebo tablets.

Number of participant	62 in total, 30 in imipramine group, 32 in placebo group.
Inclusion/Exclusion Criteria	Inclusion: aged over 6 years at one of 2 orphanages run by an Augustinian Order
Patient Characteristics	14 out of 62 were boys. The age range was 6 to 18 years. In the imipramine group the baseline wetting was 62% and in the placebo group the baseline wetting was 66%. Boys were sent to another institute at the age of 12 years. Therefore the over 12 years group contained only girls.
Recruitment	From single sex institutes.
Setting	Single sex orphanages, Durban.
Interventions/ Test/ Factor being investigated	Group A: imipramine (25mg for children aged under 12 years, 50 mg for children aged over 12 years) Group B: placebo
Comparisons	Between imipramine and placebo.
Length of Study/ Follow-up	Not reported.

Outcome measures studied	Mean number of wet nights. Drop outs.
Results	20 nights of treatment for each. Mean number of wet nights per week at the end of treatment: (data obtained from cochrane review as paper presented data in an unusable format - only first arm of treatment is presented). The imipramine group had a mean number of wet nights of 2.52, and the placebo group had a mean number of wet nights of 3.3. 2 dropped out of the imipramine group The paper presented data that showed group one, who had imipramine then placebo, had 62.3% wet nights during the observation period, 36% wet nights during imipramine treatment, 39% wet nights during placebo treatment and 55.6% wet nights in the final observational treatment. The group which received placebo then imipramine had 65.9% wet nights during the observational period, 47.2% wet nights during the placebo treatment, 36.1% wet nights during the imipramine treatment and 56.3% wet nights during the final observational treatment.
Safety and adverse effects	None reported.
Does the study answer the question?	The study shows that children treated with imipramine had fewer wet nights compared to those treated with a placebo
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies comparing imiparmine and placebo.
Directly applicable to guideline population?	Children were aged 6 to 17 years. Only girls were included in the 12 to 17 years group.
Internal Validity	Unclear allocation concealment and blinding

Hodes C;

Enuresis--a study in general practice

Ref ID 1741 1973

Study Type	Randomised Controlled Trial	**Funding**	Geigy Pharmaceuticals supported the study

Number of participant	74 in total, 36 in imipramine group, 38 in placebo group.
Inclusion/Exclusion Criteria	Inclusion: responded to a postal questionnaire, aged 5 to 15 years. Exclusion:
Patient Characteristics	The age range was 5 to 15 years. 57 out of the original 99 patients were males.
Recruitment	Questionnarie was sent to all parents with children aged 5 to 15 years at a GP practice in London.
Setting	GP practice, London, UK
Interventions/ Test/ Factor being investigated	Group A: imipramine (25 mg if aged under 6 years, 50 mg if aged over 6 years) Group B: placebo
Comparisons	Between imipramine and placebo.

Length of Study/ Follow-up	No follow up.
Outcome measures studied	Number of children who achieved 14 consecutive dry nights and adverse events.
Results	Treatment was for 30 days, if the patient was not sucessful they could repeat this for 5 1/2 months until cured or until the family decided to stop. Number of children who achieved 14 consecutive dry nights: 7 out of 36 in the imipramine group achieved 14 consecutive dry nights; 6 out of 38 in the placebo group achieved 14 consecutive dry nights. Adverses events Macular rash (unclear on which treatment).
Safety and adverse effects	Macular rash (unclear on which treatment)
Does the study answer the question?	The study showed there was little difference between children treated with imipramine and those treated with placebo.
Effect due to factor in study?	Yes, although no baseline characteristics given for final study population.
Consistency of results with other studies?	Similar to other studies comparing imipramine and placebo.
Directly applicable to guideline population?	Children aged 5 to 15 years.
Internal Validity	Unclear allocation concealment and blinding

Khorana AB;

Controlled trial of imipramine hydrochloride on enuresis

Ref ID 1743 1972

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	100 in total, 50 in group A (imipramine), 50 in group B (placebo)
Inclusion/Exclusion Criteria	Inclusion: consecutive children with primary enuresis. Exclusion: physical or neurological disorder, severe mental retardation, or unco-operative.
Patient Characteristics	74 out of the initial 100 patients were male. The mean age was 8.2 years and the age range was 5 to 15 years.
Recruitment	Psychiatric inpatients in India.
Setting	psychiatric inpatients in india
Interventions/ Test/ Factor being investigated	Group A: imipramine hydrochloride (25 mg, if aged under 10 years. If no response dose was raised to 50mg. If aged over 10 years and no response dose was raised to 75mg) Group B: placebo
Comparisons	Between imipramine and placebo.
Length of Study/ Follow-up	None
Outcome measures studied	Drop outs, number who achieved 14 consecutive dry nights, and adverse events.

Results	Treatment was for 12 weeks Number of children who achieved 14 consectuive dry nights: 19 out of 42 children in group A (imipramine) achieved 14 consecutive dry nights; 0 out of 34 in group B (placebo) achieved 14 consecutive dry nights. Adverse events: None which required treatment.
Safety and adverse effects	None which required treatment.
Does the study answer the question?	Imipramine is more effective than placebo.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies comparing imiparmine to placebo.
Directly applicable to guideline population?	Children were aged 5 to 15 years.
Internal Validity	Unclear allocation concealment and blinding

Kolvin I;Taunch J;Currah J;Garside RF;Nolan J;Shaw WB;

Enuresis: a descriptive analysis and a controlled trial

Ref ID 349 1972

Study Type Randomised Controlled Trial **Funding** Partially funded by Geigy

Number of participant	94 in total, 35 in group A, 32 in group B and 27 in group C
Inclusion/Exclusion Criteria	Inclusion: aged between 8 and 10 years
Patient Characteristics	The mean age was 9 years and 4 months. Most of the patients had poor toilet facilities, with 35 patients having out-door toilets. The mean number of children per family was 3.9. 14 children had divorced parents. 44 patients had siblings who had had enuresis and 59 had family members who had had enuresis.
Recruitment	Through a survey of schools.
Setting	At home.
Interventions/ Test/ Factor being investigated	Group A: imipramine Group B: alarm (pad and buzzer) Group C: placebo
Comparisons	Between groups A, B and C
Length of Study/ Follow-up	4 months.
Outcome measures studied	Mean number of wet nights.
Results	10% of patients were lost at 4 month follow up. The number of chidlren who had greater than 80% improvement in number of dry

	nights: In the imipramine group 16 out of 35 children achieved a greater than 80% improvement in the number of dry nights compared to 17 out of 32 in alarm group. Mean number of wet nights at the end of treatment: In the imipramine group the mean number of wet nights was 2.3 (sd 3.5) compared to alarm 2.3 (sd 3.2) Mean number of wet nights at follow up: In the imipramine group the mean number of wet nights at follow up was 3.35 (sd 3) compared to 2.3 (sd 2.3) in the alarm group.
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that the alarm group was slow to improve but maintained improvement after treatment was stopped. The imipramine group had a rapid improvement initially but a large decline after treatment was stopped. The placebo group's improvement was seen to remain after treatment was stopped.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies with same comparison.
Directly applicable to guideline population?	Children were aged between 8 and 10 years.
Internal Validity	Unclear allocation concealment and blinding.

Lake B;

Controlled trial of nortriptyline in childhood enuresis

Ref ID 567 1968

Study Type	Randomised Controlled Trial	**Funding**	Dista Products provided nortriptyline and placebo and a grant-in-aid.

Number of participant	Crossover trial with 54 in total.
Inclusion/Exclusion Criteria	Inclusion: aged 5 to 12 years, and wet at least 2 nights out of 14 nights.
Patient Characteristics	Age range 5 to 12 years and 37 out of 54 were male. The mean baseline wetting for the nortripyline group was 62% and for the placebo group was 72%. 41 were deep sleepers, 16 came from emotionally disturbed homes, 9 suffered excessive threat, 5 had previous UTI, 17 had parents who were enuretic, and 35 had enuretic siblings.
Recruitment	From nine GP practices.
Setting	GP practices
Interventions/ Test/ Factor being investigated	Group A: nortriptyline Group B: placebo
Comparisons	Nortriptyline compared to placebo
Length of Study/ Follow-up	No follow up.
Outcome measures studied	Number of wet nights per week and side effects.

Results	Patients were split into two groups. Each group received 2 weeks of each treatment with a 2 week washout. Each group had 2 sets of treatments. That is, 16 weeks in total Some results obtained from Cochrane review. Number of wet nights during treatment per week: In the nortriptyline group the mean number of wet nights was 3.56, while in the placebo group the mean number of wet nights was 4.39. Side effects: Nortriptyline - one child had a headache, aching arms and sore tummy. Placebo - 1 child had headache and vomiting, 1 had drowsiness in the car which they never had before, and 11 had dry mouth and sweating.
Safety and adverse effects	Nortriptyline - one child had a headache, aching arms and sore tummy. Placebo - 1 children had headache and vomiting, 1 had drowsiness in the car which they never had before, and 11 had dry mouth and sweating.
Does the study answer the question?	Study compared nortriptyline to placebo to show children treated with nortriptyline had fewer wet nights compared to those treated with placebo.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged 5 to 12 years.
Internal Validity	Unclear allocation concealment and blinding

Lee T;Suh HJ;Lee HJ;Lee JE;

Comparison of effects of treatment of primary nocturnal enuresis with oxybutynin plus desmopressin, desmopressin alone or imipramine alone: a randomized controlled clinical trial

Ref ID 74 2005

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	145 in total: 48 in group A, 49 in group B and 48 in group C.
Inclusion/Exclusion Criteria	Inclusion: at least 3 wet nights a week Exclusion: organic causes of NE, drug treatment in previous 14 days
Patient Characteristics	100 out of 145 were male, 53% had day time wetting (77 patients). The mean age was 7.8 years (SD 2.5), the age range was 5-15 years, and mean baseline wetting was 6.36 (SD 1.5) nights a week.
Recruitment	Not reported.
Setting	2 hospitals, between 2003 and 2004.
Interventions/ Test/ Factor being investigated	Group A: 0.1 or 0.2 md desmopressin and 5 mg oxybutinin Group B: 0.2 mg desmopressin (increased to 0.4 mg if no response) Group C: 25 mg imipramine
Comparisons	Between treatment groups
Length of Study/ Follow-up	None
Outcome measures studied	0-1 wet nights a month, drop out, mean number of wet nights, and continued response (at 3 and 6 months).

Results	Treatment was for 6 months, all treatments were given orally before bedtime Drop outs for all patients: 13 in total 3 in group A (desmopressin and oxybutylinin), 3 in group B (desmopressin) and 7 in group C (imipramine) Patients with night time wetting only: Mean number of wet nights per week at end of treatment: In group A (desmopressin and oxybutylin) the mean number of wet nights was 0.93 (SD 1.35), in group B (desmopressin) the mean number was 0.7 (SD 0.95) and in group C (imipramine) the mean number was 2.0 (2.05) Number of children with 0-1 wet nights per month: In group A (desmopressin and oxybutylin) 14 out of 22 had 0-1 wet nights per month compared to 14 out of 23 in group B (desmopressin) and 3 out of 23 in group C (imipramine). Patients with night and day time wetting: Mean number of wet nights per week at end of treatment: In group A (desmopressin and oxybutylin) the mean number of wet nights was 1.2 (SD 1.55), in group B (desmopressin) the mean number was 1.23 (SD 0.88) and in group C (imipramine) the mean number was 2.63 (2) Number of children with 0-1 wet nights per month: In group A (desmopressin and oxybutylin) 9 out of 26 had 0-1 wet nights per month compared to 9 out of 26 in group B (desmopressin) and 3 out of 25 in group C (imipramine). The mean number of wet nights continued to be reduced For the imipramine group the mean baseline wetting was 13.2 (sd 2.9) wet nights per 2 weeks, at 1 month the mean number of wet nights was 17.5 (sd 10.5) per 2 weeks, at 3 months was 11.6 (sd 10) nights per 2 weeks and at 6 months was 9.3 (sd 8.3) nights per 2 weeks. For the desmopressin group the mean baseline wetting was 12 (sd 3.5) wet nights per 2 weeks, at 1 month the mean number of wet nights was 8.3 (sd 7.3) per 2 weeks, at 3 months was 4.7 (sd 5.5) nights per 2 weeks and at 6 months was 4 (sd 4.6) nights per 2 weeks. For the desmopressin combined with oxybutynin group the mean baseline wetting was 13.3 (sd 3.4) wet nights per 2 weeks, at 1 month the mean number of wet nights was 6.7 (sd 7.9) per 2 weeks, at 3 months was 5.4 (sd 6.9) nights per 2 weeks and at 6 months was 3.7 (sd 5.4) nights per 2 weeks
Safety and adverse effects	None reported
Does the study answer the question?	Yes. Combination therapy (desmopressin and oxybutynin) produced the most rapid favorable clinical response regardless of symptomatic status.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Yes.
Internal Validity	Unclear allocation concealment and blinding

Manhas RS;Sharma JD;

Tofranil (imipramine) in childhood enuresis: a controlled clinical trail of tofranil (imipramine) in the treatment of 72 cases of childhood enuresis in Kashmir

Ref ID 1655 1967

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	72 in total: 29 in imipramine group, 27 in placebo group, 8 in placebo then imipramine, 8 in imipramine then placebo.
Inclusion/Exclusion Criteria	Inclusion: regular and consistent bed wetting and aged 5 to 15 years Exclusion: organic causes of NE.
Patient Characteristics	The age range was 5 to 15 years. No baseline characteristics given.
Recruitment	Not reported.
Setting	India
Interventions/ Test/ Factor being investigated	Group A: imipramine (25 mg for children aged under 12 years, 50 mg for children aged over 12 years) Group B: placebo Group C: placebo the imipramine Group D: imipramine then placebo
Comparisons	Between treatment groups.
Length of Study/ Follow-up	4 weeks.
Outcome measures studied	Complete and partial dryness, and side effects.
Results	Treatment was for 4 weeks Number of children who had complete relief 19 out of 29 had complete relief in group A (imipramine) compared to 1 out of 27 in group B (placebo). Number of children who had partial relief 6 out of 29 had partial relief in group A (imipramine) compared to 3 out of 27 in group B (placebo). Number of children who had no relief 4 out of 29 had no relief in group A (imipramine) compared to 23 out of 27 in group B (placebo). Side effects: Imipramine group: 3 children had abdominal pain, 2 had giddiness, 1 had dry mouth, 1 had headache, 1 had abdominal pain and epistaxis. Placebo group:1 had giddiness. No results were given for groups C and D (cross over groups)
Safety and adverse effects	Imipraimne group: 3 children had abdominal pain, 2 had giddiness, 1 had dry mnouth, 1 had headache, 1 had abdominal pain and epistaxis Placebo group: 1 had giddiness
Does the study answer the question?	
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies comparing imipramine to placebo.
Directly applicable to guideline population?	Children were aged 5 to 15 years.
Internal Validity	Unclear allocation concealment and blinding

Martin GI;

Imipramine pamoate in the treatment of childhood enuresis. A double-blind study

Ref ID 541 1971

Study Type Randomised Controlled Trial **Funding** Geigy Pharmaceuticals, Ardsley, NY

Number of participant	57
Inclusion/Exclusion Criteria	Inclusion: 3 wet nights per week for more than 6 months. Exclusion: organic causes of NE, organic heart disease, hyperthyroidism, glaucoma, diabetes, kidney or liver disease, those taking thyroid, MAO inhibitors, or anticholinergic.
Patient Characteristics	42 out of 57 were boys, and the age range was 5 to 15 years. 3 were aged 4 to 6 years, 12 were aged 6 to 8 years, 18 were aged 8 to 10 years, 16 were aged 10 to 12 years, 4 were aged 12 to 14 years, 4 were aged 14 to 15 years. Baseline mean number of wet nights in 26 nights was 20.7.
Recruitment	Not reported
Setting	Not reported
Interventions/ Test/ Factor being investigated	Group A: 10 mg imipramine pamoate (suspension) Group B: 25 mg imipramine pamoate (suspension) Group C: placebo all treatments were given 1 hour before bed time.
Comparisons	Between treatment groups.
Length of Study/ Follow-up	None
Outcome measures studied	Mean number of wet nights. Number of drop outs. Number ofside effects.
Results	26 days of each treatment Mean number of wet nights in 26 nights: The 10 mg imipamine group had a mean number of wet nights of 13.7 (sd 4.12), the 25 mg imipramine group had a mean number of wet nights of 10.5 (sd 6.03), and the placebo group had a mean number of wet nights of 16.8 (sd 6.49). There were no drop outs. Side effects: In the 25 mg imipramine group: 4 children had anxiety, 3 had sleep disturbances, 1 had abdominal pain In the 10 mg imipramine group: 2 children had anxiety, 1 had constipation, 5 had sleep disturbances, 1 had abdominal pain, 2 lost weight In the placebo group: 1 child had anxiety, 1 had constipation, 3 had sleep disturbances, 1 had abdominal pain, and 2 lost weight.
Safety and adverse effects	In the 25 mg imipramine group : 4 children had anxiety, 3 had sleep disturbances, and 1 had abdominal pain. In the 10 mg imipramine group: 2 children had anxiety, 1 had constipation, 5 had sleep disturbances, 1 had abdominal pain, and 2 lost weight. In the placebo group: 1 child had anxiety, 1 had constipation, 3 had sleep disturbances, 1 had abdominal pain, and 2 lost weight.
Does the study answer the question?	The study compared 25 mg imipramine to 10 mg imipramine and placebo, to show that 25 mg was the most effective treatment. 10 mg was also more effective than placebo.
Effect due to factor in study?	Yes

Consistency of results with other studies?	Results are similar to other studies comparing imipramine to placebo.
Directly applicable to guideline population?	Children were aged 5 to 15 years.
Internal Validity	Unclear allocation concealment and blinding

Poussaint AF;Ditman KS;

A controlled study of Imipramine (Tofranil) in the treatment of childhood enuresis

Ref ID 1661 1965

Study Type Randomised Controlled Trial **Funding** Not stated.

Number of participant	54 children were selected for treatment. 47 were treated and 7 were excluded (5 withdrew). N=13 in group 1, n=13 in group 2, n=10 in group 3 and n=11 in group 4.
Inclusion/Exclusion Criteria	Inclusion criteria: high-frequency enuretic children; all had normal urinalyses (except one with diabetes who had it in good control). No organic factors to account for the enuresis. Exclusion criteria: Those who were infrequently enuretic - e.g once per week.
Patient Characteristics	Aged 5 to 16 years old. 11 of the patients who were selected were female and 43 male. High frequency eneuretic children.
Recruitment	10 were selected from pediatric and psychiatric clinic files. 44 were referred by private physicians.
Setting	Not explicit but maybe outpatients at UCLA, USA.
Interventions/ Test/ Factor being investigated	The children were allocated to four groups who received treatment for 8 weeks: 1. Imipramine (4 weeks), then placebo (4 weeks) - 13 patients. 2. Placebo (4 weeks), then imipramine (4 weeks) - 13 patients. 3. Imipramine (4 weeks), then imipramine (4 weeks) - 10 patients. 4. Placebo (4 weeks), then placebo (4 weeks) - 11 patients.A medical and social history was given by the parents; The parents and child were shown how to chart the time of dosage of medication (1/2 to 1 hour before bedtime) and to record 'wet' and 'dry' nights on the forms provided; When prescriptions were refilled (every week or two) the parents were to return the completed forms; on these occasions there were also 10-15 minute interviews with parents to discuss the treatment results, including side effects (the children were not seen unless indicated). The hospital pharmacy dispensed imipramine (coded drug) and placebo. Dosages were fixed at 25mg of imipramine for children under 12 years and 50mg for children 12 or over.
Comparisons	Crossover study four groups: 1. Treatment followed by placebo. 2. Placebo followed by treatment. 3. Treatment followed by treatment. 4. Placebo followed by placebo.
Length of Study/ Follow-up	8 weeks. End of study treatment period.
Outcome measures studied	Number of wet nights in each 4 week period of treatment compared to the average frequency of wet nights reported for the 4 week period prior to treatment and rated on a scale. Side effects.
Results	There were 7 drop-outs (5 withdrew, 2 excluded) - some could not swallow the tablets, or feared the drugs; one developed a bladder infection while receiving the placebo and one appeared to be psychotic.

	Results from Cochrane as results in paper was in graph form: For the crossover trial: Imipramine was better than placebo in 69%, equal in 23% and the placebo was better than drug in 8% (p<0.0005). No. of children totally dry: imipramine group=6, placebo group=1 (no relapses). Only relapses were when medication abruptly withdrawn - all had medication restored. Side effects: more irritable (8) dizziness (1), dry mouth (1), decreased appetite (1) - similar complaints were reported by children receiving placebo (for the last three side effects). When the 8 week period was finished all of the children who were still wet received an increased dose of 75mg. Eleven children became completely dry and remained so after imipramine was gradually withdrawn following 2 months of complete dryness with the medication. The only patients who relapsed were those in whom the medication was abruptly withdrawn. Therefore in follow up 24% of children were 'cured' by imipramine.
Safety and adverse effects	None stated. Each parent signed a consent form which outlined the side effects of imipramine.
Does the study answer the question?	Imipramine (a trycyclic) was shown to be more beneficial than placebo in showing a decrease in enuretic nights.
Effect due to factor in study?	No.
Consistency of results with other studies?	Similar to other studies comparing imipramine and placebo.
Directly applicable to guideline population?	Direct.
Internal Validity	Unclear allocation concealment and blinding.

Smellie JM;McGrigor VS;Meadow SR;Rose SJ;Douglas MF;

Nocturnal enuresis: a placebo controlled trial of two antidepressant drugs

Ref ID 309 1996

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	80 in total 25 in imipramine group, 26 in mianserin and 29 in placebo group.
Inclusion/Exclusion Criteria	Inclusion: Exclusion: organic causes of NE
Patient Characteristics	In the imipramine group 19 out of 25 were boys and in the placebo group 24 out of 29 were boys. Age range was 5 to 13 years. In the imipramine group 9 were aged 5 to 6 years, 7 were aged 7 to 9 years, 9 were aged 10 to 13 years; in the placebo gorup 10 were aged 5 to 6 years, 12 were aged 7 to 9 years and 7 were aged 10 to 13 years. The baseline mean number of dry nights per week was 1.6 in the imipramine group and 1 in the placebo group.
Recruitment	Participants were referred from hospital or community child health enuretic clinics by GP, paediatricians, paediatric urologists or school doctors.
Setting	UK
Interventions/ Test/ Factor being investigated	Group A: 25mg imipramine Group B: placebo Study also considered mianserin which is not included in this review

Comparisons	Comparison is between imipramine and placebo.
Length of Study/ Follow-up	4 weeks
Outcome measures studied	Mean number of dry nights.
Results	Data presented in graphs - figures obtained from cochrane review Treatment for 8 weeks Mean number of dry nights in week 6: The imipramine group had a mean number of dry nights of 5, and the mean number of dry nights for the placebo group was 2.5. Mean number of wet nights: In the imipramine group the mean number of wet nights was 2 compared to 4.5 in the placebo group. % of patients who had improvement after 4 weeks without treatment (follow up): 74% in the imipramine had improvement after 4 weeks compared to 59% in the placebo group.
Safety and adverse effects	None reported
Does the study answer the question?	Study compared imipramine to placebo and results showed that more children in the imipramine group achieved 7 dry nights and continued to show improvement after 4 weeks follow up.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies comparing imipramine and placebo.
Directly applicable to guideline population?	Children were aged 5 to 13 years
Internal Validity	Unclear allocation concealment and blinding

Tahmaz L;Kibar Y;Yildirim I;Ceylan S;Dayanc M;

Combination therapy of imipramine with oxybutynin in children with enuresis nocturna

Ref ID 201 2000

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	77 in total: 14 in Group A, 16 in Group B, 24 in Group C and 23 in Group D.
Inclusion/Exclusion Criteria	Inclusion: primary monosymptomatic NE, wet at least 3 nights a week,and no current treatment Exclusion: organic causes of NE, day time wetting, or UTI.
Patient Characteristics	48 out of 77 were boys. The mean age was 9.44 (SD 2.17) years (range 6-14 years).
Recruitment	Patients at Dept Urology, Military Medical Faculty, Turkey.
Setting	Dept Urology, Military Medical Faculty, Turkey
Interventions/ Test/ Factor being investigated	Group A (14) imipramine 0.9-1.5 mg/kg/day B (16): oxybutinin 5 mg 3x/day C (24): imipramine + oxybutinin D (23): placebo (not described)

Comparisons	Between treatment groups.
Length of Study/ Follow-up	6 months
Outcome measures studied	Achievement of >90% reduction in number of wet nights, relapse at 6 months, adverse events, drop outs
Results	3 months of treatment. >90% reduction in number of wet nights: 7 out of 14 in group A (imipramine) achieved >90% reduction in wet nights compared to 6 out of 16 in group B (oxybutinin), 16 out of 24 in group C (imipramine and oxybutinin) and 5 out 23 in group D (placebo) Relasped at 6 months: In group A (imipramine) 5 out of 7 had relapsed at 6 months compared to 5 out of 6 in group B (oxybutinin), 4 out of 16 in group C (imiprmaine and oxybutinin) and 2 out of 5 in group D (placebo). 50% improvement 5 out of 14 in group A, 6 out of 16 in group B, 6 out of 24 in group C and 8 out of 23 in group D Adverse events (dry mouth or nausea): In group A (imipramine) 3 out of 14 had adverse events compared to 4 out of 16 in group B (oxybutinin), 7 out of 24 in group C (imipramine and oxybutinin) and 4 out of 23 in group D (placebo) If completely cured patients were slowly taken off treatment.
Safety and adverse effects	18 children had adverse events
Does the study answer the question?	All drug treatments were more effective than placebo. Imipramine combined with oxybutinin was most effective.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Consistent with other similar studies.
Directly applicable to guideline population?	Age range 6-14 years.
Internal Validity	Unclear allocation concealment and blinding

Treffert DA;

An evaluation of imipramine in enuresis

Ref ID 1663 1964

Study Type	Randomised Controlled Trial	**Funding**	Geigy Pharaceuticals supplied imipramine and placebo

Number of participant	9
Inclusion/Exclusion Criteria	Inclusion: NE
Patient Characteristics	All patients were boys. The mean baseline wetting was 2.9 time a week. Children were in Winebago State Hospital which is a hospital for neurotic, psychotic, brain injured boys

Recruitment	Children in Winebago State Hospital (hospital for neurotic, psychotic, brain injured boys)
Setting	Winebago State Hospital
Interventions/ Test/ Factor being investigated	Group A: imipraimne (25mg for children under 12 years, 50 mg for children over 12 years) Group B: placebo
Comparisons	between imipramine and placebo
Length of Study/ Follow-up	4 weeks
Outcome measures studied	number of wet nights
Results	Treatment for 4 weeks of each, data obtained from cochrane review Number of wet nights during treatment: In group A (imipramine) the number of wet nights was 1.86, in group B (placebo) the mean number of wet nights was 2.36.
Safety and adverse effects	None reported
Does the study answer the question?	The study comapred imipramine to placebo to show children treated with imipramine had fewer wet nights per week compared to children treated with placebo
Effect due to factor in study?	Yes
Consistency of results with other studies?	Similar to other studies comparing imiparmine and placebo
Directly applicable to guideline population?	Children were aged 6 to 18 years
Internal Validity	Unclear allocation concealment and blinding

Vertucci P;Lanzi C;Capece G;Fano M;Gallai V;Margari L;Mazzotta G;Menegati E;Ottaviano S;Perini A;Perniola T;Roccella M;Tiberti A;Vecchio A;Biraghi M;

Desmopressin and imipramine in the management of nocturnal enuresis: a multicentre study

Ref ID 297 1997

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	57 in total, 29 who received desmorpessin then imipramine, 28 who received imipramine then desmopressin.
Inclusion/Exclusion Criteria	Inclusion: primary NE aged over 5 years, wet at least 3 nights a week, and parental consent. Exclusion: organic or neurological dysfunction of the urinary system.
Patient Characteristics	The age range was 6 to 15 years. The mean age was 10 years. 37 out of 57 were male.
Recruitment	Children at Child Neuropsychiatry clinics in Italy
Setting	Child Neuropsychiatry Clinics Italy
Interventions/ Test/ Factor being investigated	Group A: Desmopressin 30 mcg intranasal then imipramine 0.9 mg/kg Group B: Imipramine 0.9 mg/kg then desmopressin 30 mcg intranasal

Comparisons	Between desmopressin and imipramine.
Length of Study/ Follow-up	2 weeks (observation period), 3 weeks treatment period.
Outcome measures studied	Number of wet nights, 14 consecutive dry nights, drop outs, and side effects.
Results	Data was presented in graphs - data presented below was from Cochrane review Treatment was for 3 weeks of each. Mean number of wet nights during first arm of trial In Group A (desmopressin) the mean number of wet nights was 1, in Group B (imipramine) the mean number of wet nights was 2.8. Number who achieved 14 consecutive dry nights: 25 out of 29 achieved 14 consecutive dry nights when treated with desmopressin compared to 19 out of 28 who were treated with imipramine. Mean number of wet nights after both drugs had been used: In group A (desmopressin then imipramine) the mean number of wet nights was 3.5 compared to 2.8 in group B (imipramine then desmopressin). Drop outs: 5 in total Side effects: Desmopressin:1 had back pain, 1 had a an inflamed nasal mucosa Imipramine: 1 had pallor, restlessness and cold extremities
Safety and adverse effects	Desmopressin: 1 had back pain, 1 had a an inflamed nasal mucosa Imipramine: 1 had pallor, restlessness and cold extremities
Does the study answer the question?	Study compared desmorpessin to imipramine to show that both reduced the number of wet nights. However desmopressin was more effective than imipramine.
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	Children were aged 6 to 15 years.
Internal Validity	Unclear allocation concealment and blinding

Wagner W;Johnson SB;Walker D;Carter R;Wittner J;

A controlled comparison of two treatments for nocturnal enuresis

Ref ID 143 1982

Study Type	Randomised Controlled Trial	**Funding**	None reported.

Number of participant	49 in total, 12 in each group
Inclusion/Exclusion Criteria	Inclusion: aged 6-16 years, IQ greater than 70, primary NE, no physcial or neurological disorders, wet at least 3 times a week, no treatment for NE in previous year, and agreed to be randomised. Exclusion: day time wetting.
Patient Characteristics	The mean age was 7.9 years. The baseline % of nights wet for group A (alarm) was 75%, group B (imipramine) 77.33% and group C (waiting list) 64.33%. There was no signficant difference between groups in % of nights wet.
Recruitment	From local paediatric clinics and private physicians, adverts in newspapers and on TV, and contact with local schools

Setting	Florida, USA and treatment was administerd at home
Interventions/ Test/ Factor being investigated	Group A: alarm (pad and bell) Group B: imipramine Group C: control - no treatment, waiting list
Comparisons	Between groups A, B and C
Length of Study/ Follow-up	44 days.
Outcome measures studied	Number of patients dry for 14 consecutive nights,% of wet nights, and relapse.
Results	Treatment for 14 weeks or until dry for 14 nights There were no results for the alarm and placebo group Dry for 14 consecutive nights: In group A (alarm) 10 out of 12 achieved dryness for 14 consecutive nights compared to 4 out of 12 in group B (imipramine) and 1 out of 12 in group C (waiting list) % of wet nights: The study showed that by the final treatment week, group A was significantly more sucessful than B and C (8.25% compared to 39.25% and 60.83%) Relapse: Relapse was defined as 3 wet nights in a 2 week period. Of the children who achieved 14 nights dry In group A (alarm) 5 out of 10 relapsed compared to 4 out of 4 in group B (imipramine) and 1 out of 1 in group C (waiting list).
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that giving a child an alarm was more sucessful than imipramine and a control waiting list group in achieving 14 dry nights (83% compared to 33% and 8%). The study also showed that the patients receiving alarm therapy had only a 50% relapse rate compare to 100% in both the imipramine group and waiting list group.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	Similar to other studies with same comparison.
Directly applicable to guideline population?	Age range 6-16 years.
Internal Validity	Unclear allocation concealment and blinding

Grading: 2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

Bain DJ;

A criticism of the use of tricyclic antidepressant drugs in the treatment of childhood enuresis

Ref ID 1799 1973

Study Type Cohort **Funding** Not reported

Number of participant	53 cases
Inclusion/Exclusion Criteria	Children had imipramine poisoning.
Patient Characteristics	Not reported.
Recruitment	Cases of imipramine poisoning in 1968 and 1970.
Setting	UK
Interventions/ Test/ Factor being investigated	Imipramine
Comparisons	No comparison
Length of Study/ Follow-up	Not reported
Outcome measures studied	Side effects
Results	In 1968 17 cases of poisoning were reported and in 1970 there were 36 cases. The study reported one author collected the reason for 20 deaths in children from imipramine poisoning. Only one of these was from a drug prescribed for the child who had nocturnal enuresis.
Safety and adverse effects	Imipramine poisoning.
Does the study answer the question?	In 1968 17 cases of imipramine poisoning were reported, and in 1970 there were 36 cases.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	
Directly applicable to guideline population?	Patients were not all being treated for NE.
Internal Validity	Adequately addressed

Goel KM;Shanks RA;

Amitriptyline and imipramine poisoning in children

Ref ID 1773 1974

Study Type	Cohort	**Funding**	Not reported.

Number of participant	60 cases reviewed
Inclusion/Exclusion Criteria	Children had amitriptyline or imipramine poisoning
Patient Characteristics	Not reported.
Recruitment	Cases of poisoning in children between January 1966 and July 1973.
Setting	UK
Interventions/ Test/ Factor being investigated	Amitriptyline or imipramine.
Comparisons	No comparison.
Length of Study/ Follow-up	Not reported.
Outcome measures studied	Side effects.
Results	The study considered cases of poisoning in children treated for NE or depression, results were not separated out. The study identified 60 cases of poisoning in total, 16 of which were from the medication prescribed for the child poisoned during the treatment of nocturnal enuresis. The study reported the cases of poisoning from amitriptyline and imipramine prescribed for the treatment of nocturnal enuresis. The study reported the cardiovascular features of poisoning (prescribed for both nocturnal enuresis and depression) but the study did not separate out the results for the two groups. From amitriptyline poisoning 24 children had sinus tachycardia, 2 children had sinus arrhythmia, 2 children had ventricular premature systole, 0 children had conduction disturbances, 1 child had hypotension and 1 child had cardiorespiratory arrest. From imipramine poisoning 12 children had sinus tachycardia, 2 children had sinus arrhythmia, 1 child had ventricular premature systole, 2 children had conduction disturbances, 2 children had hypotension and 2 children had cardiorespiratory arrest. The study also reported neurological and atropinic features of poisoning, from amitriptyline 36 patients had drowsiness, 17 had agitation and / or restlessness, 16 had ataxis, 5 had mydriasis, 9 had vomiting, 8 had flushing of the face, 1 had coma, 6 had convulsions, 4 had hyperrefexia, 2 had retention of urine, 3 had hallucinations, 1 had dysarthria and 2 had nystagmus. From imipramine 12 patients had drowsiness, 7 had agitation and / or restlessness, 1 had ataxis, 8 had mydriasis, 3 had vomiting, 3 had flushing of the face, 2 had coma, 2 had convulsions, 1 had hyperrefexia, 2 had retention of urine, 0 had hallucinations, 1 had dysarthria and 0 had nystagmus. The study did not report the doses of the medication prescribed or taken.
Safety and adverse effects	Cardiovascular, neurological and atropinic features of poisoning by amitriptyline or imipramine.
Does the study answer the question?	The study considered cases of poisoning in children treated for NE or depression, results were not separated out.
Effect due to factor in study?	Yes.
Consistency of results with other studies?	
Directly applicable to guideline population?	The study considered cases of poisoning in children treated for NE or depression, results were not separated out.
Internal Validity	Adequately addressed

Monda JM;Husmann DA;

Primary nocturnal enuresis: a comparison among observation, imipramine, desmopressin acetate and bed-wetting alarm systems

Ref ID 978 1995

Study Type	Cohort	**Funding**	Not reported

Number of participant	44 in imipramine and 88 in desmopressin.
Inclusion/Exclusion Criteria	Inclusion: primary monosymptomatic nocturnal enuresis, and 3 or more wet nights per week Exclusion: diurnal urinary incontinence, or voiding dysfunction.
Patient Characteristics	The age range was 6 to 14 years and the median age was 9 years.
Recruitment	Attending investigators clinic.
Setting	Minnesota, USA.
Interventions/ Test/ Factor being investigated	1 mg/kg imipramine, increased to 1.5 mg/kg if still wetting after 2 weeks. Given 30 to 45 minutes before going to bed.
Comparisons	Study also considered desmopressin and alarms, however already have RCT evidence of these treatments for monosymptomatic children
Length of Study/ Follow-up	12 months
Outcome measures studied	Dry (only 0 to 1 wet nights per month), side effects
Results	6 months of treatment after which the child was weaned off the treatment over 4 weeks, by reducing the dose by half for 2 weeks, after which this dose was given every other night for a further 2 weeks then stopped Patients were required to keep a diary of wet and dry nights 0 to 1 wet nights per month: 14 out of 44 children achieved only 0 to 1 wet nights per month after 6 months of treatment At 12 month follow up 7 out of 44 children had 0 to 1 wet nights per month Side effects: 3 children reported hyperactivity
Safety and adverse effects	3 children reported hyperactivity
Does the study answer the question?	The study showed children with monosymptomatic NE treated with imipramine can become dry after 6 month of treatment.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other studies.
Directly applicable to guideline population?	Median age 9 years.
Internal Validity	Well covered

Question: What is the clinical and cost effectiveness of anticolinergic drugs for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Esmaeili M;

Combined treatment with oxybutynin and imipramine in enuresis

Ref ID 636 2008

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	89 in total: 29 in imipramine group, 26 in oxybutinin group and 34 in imipramine and oxybutinin group.
Inclusion/Exclusion Criteria	Inclusion: primary NE, wet at least 2 nights a week for preceding 3 months, never been dry for more than 6 months Exclusion: voiding dysfunction other than primary NE, urologic and neurological abnormalities, prior pharmacological treatment, UTI, or diurnal enuresis.
Patient Characteristics	The mean age was 8.9 (SD 1.6) years, age range 6-14 years. The mean baseline wetting was 5.1 (SD 1.1) nights per week.
Recruitment	Patients were referred to the pediatric nephrology clinic at Mashhad University of Medical Sciences between November 2003 and March 2004.
Setting	Iran
Interventions/ Test/ Factor being investigated	Group A: 10-25 mg imipramine Group B: 3.75-5 mg oxybutinin Group C: imipramine and oxybutinin
Comparisons	Between treatment groups
Length of Study/ Follow-up	1 month
Outcome measures studied	Dry for 14 consecutive nights, mean number of wet nights per week during treatment
Results	1 month of treatment Number of children who achieved 14 consecutive dry nights: 4 out of 29 children in group A (imipramine) group were cured, compared to 6 out of 26 in group B (oxybutinin) and 14 out of 34 in group C (imipramine and oxybutinin). The mean number of wet nights per week during treatment: The mean number of wet nights per week during treatment was 3.5 (SD 2) for group A (imipramine), the mean for group B (oxybutinin) was 2.5 (SD 1.7) and for group C (imipramine and oxybutinin) the mean was 1.4 (SD 1.5)
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed that the most effective treatment was imipramine combined with oxybutinin.
Effect due to factor in study?	Yes
Consistency of results with other studies?	Consistent with other similar studies.
Directly applicable to guideline population?	Age range 6-14 years.
Internal Validity	Unclear allocation concealment and blinding

Tahmaz L;Kibar Y;Yildirim I;Ceylan S;Dayanc M;

Combination therapy of imipramine with oxybutynin in children with enuresis nocturna

Ref ID 201 2000

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	77 in total (Group A n=14, group B n=16, Group C n=24, Group D n=23)
Inclusion/Exclusion Criteria	Inclusion: primary monosymptomatic NE, wet at least 3 nights a week, and no current treatment. Exclusion: organic causes of NE, day time wetting, or UTI.
Patient Characteristics	48 out of 77 were boys. The mean age was 9.44 (SD 2.17) years (range 6-14 years).
Recruitment	Patients at Dept Urology, Military Medical Faculty, Turkey
Setting	Dept Urology, Military Medical Faculty, Turkey
Interventions/ Test/ Factor being investigated	Group A (14) imipramine 0.9-1.5 mg/kg/day B (16): oxybutinin 5 mg 3x/day C (24): imipramine + oxybutinin D (23): placebo (not described)
Comparisons	Between treatments.
Length of Study/ Follow-up	6 months
Outcome measures studied	>90% reduction in number of wet nights, 50-90% improvement in number of dry nights, relapse at 6 months, and adverse events.
Results	3 months of treatment. >90% reduction in number of wet nights: 7 out of 14 in group A (imipramine) achieved >90% reduction in wet nights compared to 6 out of 16 in group B (oxybutinin), 16 out of 24 in group C (imipramine and oxybutinin) and 5 out 23 in group D (placebo). 50-90% reduction in number of wet nights: 5 out of 14 in group A (imipramine) achieved 50-90% reduction in wet nights compared to 6 out of 16 in group B (oxybutinin), 6 out of 24 in group C (imipramine and oxybutinin) and 8 out 23 in group D (placebo). Relasped at 6 months: In group A (imipramine) 5 out of 7 had relapsed at 6 months compared to 5 out of 6 in group B (oxybutinin), 4 out of 16 in group C (imipramine and oxybutinin) and 2 out of 5 in group D (placebo). Adverse events (dry mouth or nausea): In group A (imipramine) 3 out of 14 had adverse events compared to 4 out of 16 in group B (oxybutinin), 7 out of 24 in group C (imipramine and oxybutinin) and 4 out of 23 in group D (placebo). If completely cured, patients were slowly taken off treatment.
Safety and adverse effects	18 children had adverse events
Does the study answer the question?	All drug treatments were more effective than placebo. Imipramine combined with oxybutinin was most effective.
Effect due to factor in study?	Yes

Consistency of results with other studies?	Consistent with other similar studies.
Directly applicable to guideline population?	Age range 6-14 years.
Internal Validity	Unclear allocation concealment and blinding

Question: What is the clinical and cost effectiveness of information and educational interventions for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Redsell SA;Collier J;Garrud P;Evans JH;Cawood C;

Multimedia versus written information for nocturnal enuresis education: a cluster randomized controlled trial

Ref ID 1753 2003

Study Type	Randomised Controlled Trial	**Funding**	Trent region NHS executive, UK.

Number of participant	270 in total, 108 in Group A (the "CD" group), 87 in Group B (the "Written" group), and 75 in Group C (the "Alarm only").
Inclusion/Exclusion Criteria	Inclusion: primary or secondary NE. Exclusion: treatment for NE in previous 6 months.
Patient Characteristics	Mean age 7.98 years (sd 2.23) and age range 5 to 16 years. 176 out of 270 were male, 90.3% had primary NE, and 20.7% had secondary NE.
Recruitment	Schools.
Setting	School nurse-led enuresis clinics Leicestershire.
Interventions/ Test/ Factor being investigated	Group A: multimedia CD rom, “all about nocturnal enuresis” to use which had 10 minute modules on “welcome to the clinic, how your bladder works, why some children wet the bed, boss of your bladder, treatments, information for grown ups, knowledge tree”, children were given a suggested order to watch the modules in Group B: written leaflets, 6 leaflets with same information as the CD rom Group C: control group All children had 4 weeks of star charts and then alarm treatment
Comparisons	Between groups
Length of Study/ Follow-up	6 months
Outcome measures studied	Number of children who achieved 14 consecutive dry nights, number of children who relapsed at 6 months
Results	6 months of treatment Number of children who achieved 14 consecutive dry nights: In Group A (CD rom) 51 out of 108 children achieved 14 consecutive dry nights compared to 41 out of 87 in Group B (written) and 36 out of 75 in Group C (alarm alone). Number of children who failed or relapsed at 6 months: In Group A (CD rom) 30 out of 51 children relapsed compared to 15 out of 41 in Group B (written) and 18 out of 36 in Group C (alarm alone)
Safety and adverse effects	None reported.
Does the study answer the question?	The study showed there was no statistically significant difference between the two types of information. However children who had the CD rom were more likely to relapse at 6 months.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other studies considered educational interventions.

Directly applicable to guideline population?	Patients had a mean age of 7.98 years.
Internal Validity	Unclear allocation concealment and blinding

Question: What is the clinical and cost effectiveness of psychological interventions for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Iester A;Marchesi A;Cohen A;Iester M;Bagnasco F;Bonelli R;

Functional enuresis: pharmacological versus behavioral treatment

Ref ID 384 1991

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	168 in total, 36 in Group A (imipramine), 36 in Group B (3 step program) and 96 in Group C (counselling, 3 step program and education).
Inclusion/Exclusion Criteria	Inclusion: functional enuresis. Exclusion: organic causes of NE or emotional disturbance.
Patient Characteristics	The age range was 6 to 11 years.
Recruitment	Patients seen between 1979 and 1988.
Setting	Genoa University, Genova, Italy.
Interventions/ Test/ Factor being investigated	Group A: imipramine for 6 weeks 0.9-1.5mg/kg maximum dosage 50 mg Group B: 3 step program of reassurance to parents, bladder control training and waking with an alarm clock before micturition, parental involvement Group C: motivational therapy and 3 step program
Comparisons	Between treatment groups.
Length of Study/ Follow-up	12 month follow up.
Outcome measures studied	Number of children who achieved 14 consecutive dry nights,and relapse after 12 months.
Results	Children in the three step program (Group B) had 1) reassurance to the parents and tried to encourage the child; 2) bladder retention training (drink more during the morning and afternoon, reduce the number of times voided during the day, trying to hold for at least 8 hours and interrupt voiding – stop start training) and behaviour training (drink as little as possible after 7 pm, urinate bedfore going to bed and wake up once or twice using an alarm clock); 3) parents were involved in the treatment to help the child practice and avoid family conflicts. Children in the motivation therapy group (Group C) had the 3 step program as described and motivational therapy where children, in a group, discussed their problems with a psychiatrist. Treatment was for 6 months. Number of children who achieved 14 consecutive dry nights In Group A (imipramine) 14 out of 36 achieved 14 consecutive dry nights compared to 24 out of 36 in Group B (3 step program) and 81 out of 96 in Group C (counselling, 3 step program and education). Relapse after 12 months In Group A (imipramine) 2 out of 14 relapsed compared to 2 out of 24 in Group B (3 step program) and 3 out of 81 in Group C (counselling, 3 step program and education).
Safety and adverse effects	None reported
Does the study answer the question?	The study showed that more children treated with counselling, 3 step program and education achieved 14 consecutive dry nights compared to imipramine or the 3 step program.
Effect due to factor in study?	Yes

Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged 6 to 11 years.
Internal Validity	Unclear alloaction concealment and blinding

Ronen T;Wozner Y;Rahav G;

Cognitive intervention in enuresis

Ref ID 370 1992

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	77 in total, 20 in Group A (counselling), 19 in Group B (alarm), 20 in Group C (star chart), 18 in Group D (waiting list).
Inclusion/Exclusion Criteria	Inclusion: aged over 5 years, children attending a community mental health clinic with primary NE. Exclusion: organic causes of NE, or mental or developmental problems.
Patient Characteristics	The mean age was 10.05 (sd 2.28) years, the mean baseline wetting over 3 weeks in Group A (counselling) was 19.8 (sd 1.73), in Group B (alarm) it was 19.8 (sd 2.14), in Group C (star chart) it was 18.9 (sd 2.21) and in Group D (waiting list) it was 18 (sd 8.72)
Recruitment	Children attending a community mental health clinic with primary NE
Setting	Israel
Interventions/ Test/ Factor being investigated	Group A: Cognitive and behavioural self-control education therapy Group B: Pad and bell alarm Group C: star chart - stars were given for a dry night Group D: waiting list
Comparisons	Between treatment groups.
Length of Study/ Follow-up	6 months follow up
Outcome measures studied	Number dry for 3 consecutive weeks, mean number of wet nights in 3 weeks at the end of treatment, failed or relapse after 6 months,and drop out rate.
Results	Stars were given as a reward for a dry night; cognitive behaviour therapy comprised parents and children being taught 5 components of “modification of misconceptions and irrational beliefs; rational analysis of bedwetting; sensitization to pressure in bladder; self-control training in different situations; exercises in self-observation, charting,. Self assessment and self-reinforcement”. Treatment was for 18 weeks Number of children who were dry for 3 consecutive weeks In Group A (counselling) 15 out of 20 children were dry for 3 consecutive weeks compared to 12 out of 19 in Group B (alarm), 6 out of 20 in Group C (star chart) and 0 out of 18 in Group D (waiting list). Mean number of wet nights in 3 weeks at the end of treatment: The mean number of wet nights over 3 weeks at the end of treatment in group A (counselling,n= 18 children) was 1.03 (sd 2.15), in Group B (alarm, n= 15 children) mean was 1.23 (sd 5.28), in Group C (star chart, n= 14 children) mean was 3.33 (sd 5.8) and in Group D (waiting list, n= 16 children) mean was 17.22 (sd 9). Number of children who failed or relapsed after 6 months In Group A (counselling) 3 out of 18 children failed or relapsed compared to 9 out of 15 in Group B (alarm) and 8 out of 14 in Group C (star chart).

	Drop out: In Group A (counselling) 2 out of 20 children dropped out compared to 4 out of 19 in Group B (alarm), 6 out of 20 in Group C (star chart) and 11 out of 18 in Group D (waiting list).
Safety and adverse effects	None reported
Does the study answer the question?	The study shows children treated with counselling or alarms were more sucessful than the other treatment groups.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children were aged over 5 years.
Internal Validity	Unclear allocation concealment and blinding

Werry JS;COHRSSEN J;

Enuresis: an etiologic and therapeutic study

Ref ID 355 1965

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	42 in total, 21 in group A, 21 in group B
Inclusion/Exclusion Criteria	Inclusion: never been dry for longer than 3 months, wet at least once a week Exclusion: organic cause of NE
Patient Characteristics	NE patients the mean age was 9.79 (2.34 SD) years and 62% were boys
Recruitment	From enuresis clinic in a peadatric outpatients clinic of the Montreal Children's Hospital
Setting	Montreal, Canada, treatment at home
Interventions/ Test/ Factor being investigated	Group A: alarm Group B: psychotherapy - 6 to 8 sessions over 3 months The study compared to non NE siblings – not a relevant comparison so not included in the question
Comparisons	Between groups A and B
Length of Study/ Follow-up	4 months
Outcome measures studied	Dry for 14 consecutive nights, psychologic effects
Results	Treatment was until the child became dry (at least one month) or up to 4 months when the trial ended. At the end of 4 months parents were called to report how many times the child had been wet in the preceding month. 14 consecutive dry nights: In group A (alarm) 7 out of 22 children achieved 14 consecutive dry nights compared to 2 out of 21 in group B (psychotherapy) Psychological effect: There was no significant differences in the psychological changes between the

	treatment groups. The type of treatment did not affect the psychological improvement all children improved. The authors noted that alarm treatment was more economic as it required less professional input than the psychotherapy treatment.
Safety and adverse effects	None reported
Does the study answer the question?	The results showed that children treated with an alarm were more likely to be dry for a month when the results were recorded. The study also showed that the type of treatment did not affect the physiological improvement of the child.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	The mean age for NE patients was 9.79 years
Internal Validity	Unclear allocation concealment and blinding

Question: What is the clinical and cost effectiveness of alternative interventions for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Banerjee S;Srivastav A;Palan BM;

Hypnosis and self-hypnosis in the management of nocturnal enuresis: A comparative study with imipramine therapy

Ref ID 1258 1993

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	50 in total: 25 in each group
Inclusion/Exclusion Criteria	Inclusion: wet every night, and no medical or surgical cause for NE.
Patient Characteristics	30 were male, the age range was 5 to 16 years, and children were wet every night.
Recruitment	Not reported.
Setting	Not reported.
Interventions/ Test/ Factor being investigated	Group A: hypnotherapy; Group B: imipramine.
Comparisons	Between groups.
Length of Study/ Follow-up	Follow up: 1, 2, 3 and 6 months.
Outcome measures studied	Number of children who were dry or improved at 3 months, and number of chidlren who relapsed at 6 months.
Results	3 months of treatment Hypnotherapy was described as the child was first taught to relax and instructed to listen to the therapist and imagine what they were describing. They were then induced into hypnosis by techniques described by Gardner and Olness. The children were then given suggestions, again based on those described by Gardner and Olness. Children were given two 30 minutes sessions in the first week, and then one session in the second week. Further sessions depended upon the child but were between once a week and once a fortnight. Children receiving imipramine had 25 mg each night and the dose was increased each week if there was no response. Number of children who were dry or improved at 3 months: 18 out of 25 children in the hypnotherapy group were dry or improved at 3 months compared to 19 out of 25 in the imipramine group. Number of children who relapsed: 1 out of 18 children relapsed in the hypnotherapy group compared to 13 out of 19 in the imipramine group.
Safety and adverse effects	None reported.
Does the study answer the question?	The trial showed there was no statistically significant difference in the number of children who became dry or had a reduced number of wet nights between children treated with hypnotherapy and children treated with imipramine. The trial showed children treated with imipramine were more likely to relapse at 6 months compared to children treated with hypnotherapy.
Effect due to factor in study?	Yes.

Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had an age range of 5 to 16 years.
Internal Validity	Unclear alloaction concealment and blinding

Edwards SD;van d;

Hypnotherapy as a treatment for enuresis

Ref ID 449 1985

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	48 in total; 12 in each of the four groups.
Inclusion/Exclusion Criteria	Inclusion: primary or secondary NE, with no organic pathology or diurnal enuresis.
Patient Characteristics	All children were male, the mean age was 10.5 years, the mean baseline wetting for group A was 2.7, for group B was 2, for group C was 3.8 and for group D was 2.
Recruitment	Letters to boys schools.
Setting	Cape Penisula, South Africa.
Interventions/ Test/ Factor being investigated	Group A: trance with suggestions Group B: suggestions without trance Group C: trance alone Group D: waiting list
Comparisons	Between groups
Length of Study/ Follow-up	6 months
Outcome measures studied	The mean number of wet nights per week at the end of treatment and at follow upb
Results	Trance with suggestions was described as the child was induced into a trance in a special relaxing chair and listened to suggestions on a tape through headphones. Trance without suggestions was described as being induced into trance and then woken up, however the author stated due to moral reasons the children were given minimal suggestions before the trance. Suggestions without trance was described as the same procedure as trance with suggestions but without trance. Mean number of dry nights at the end of treatment: In group A the mean number ofdry nights at the end of treatment was 4.5 (trance with suggestions), compared to 4.5 in group B (suggestions without trance), 4.8 in group C (trance without suggestions) and 2.1 in group D (no treatment) Mean number of dry nights at follow up: In group A the mean number ofdry nights at follow up was 4.3 (trance with suggestions), compared to 4.6 in group B (suggestions without trance), 5.1 in group C (trance without suggestions) and 2.8 in group D (no treatment)
Safety and adverse effects	None reported.
Does the study answer the question?	The trial showed there was no difference in the mean number of wet nights per week at the end of treatment between children treated with trance with suggestions and children treated with suggestions without trance. The trial showed children treated with suggestions without trance had fewer wet nights per week at follow up compared to children treated with trance with suggestions. The trial showed children treated with trance without suggestions had fewer wet nights per week at the end of treatment and at follow up compared to children treated with trance with suggestions.

	The trial showed children treated with trance without suggestions had fewer wet nights per week at the end of treatment and at follow up compared to children treated with suggestions without trance. The study did not give standard deviation values and therefore the mean difference and CI are not estimable.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had a mean age of 10.5 years.
Internal Validity	Unclear allocation concealment and blinding

Ferrara P;Marrone G;Emmanuele V;Nicoletti A;Mastrangelo A;Tiberi E;Ruggiero A;Fasano A;Paolini P;

Homotoxicological remedies versus desmopressin versus placebo in the treatment of enuresis: a randomised, double-blind, controlled trial.

Ref ID 19 2008

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	151 patients were randomised; n=50 to desmopressin, n=50 to homotoxicological remedies and n=51 to receive placebo.
Inclusion/Exclusion Criteria	Inclusion criteria: patients aged 6-14 years, meet the International Children's Continency Society definitions of NE and no having received treatment for NE or homotoxicological remedies. Exclusion criteria: NE associated with day-time symptoms (urgency, frequency, UI, urinary tract anomalies or infections)
Patient Characteristics	All patients had ICCS definition of NE and none had received treatment for NE or homotoxicological remedies within the previous 3 months. Patients aged 6 years to 14 years (mean 8.5 years).
Recruitment	From a Department of Paediatrics in Italy
Setting	University Hospital
Interventions/ Test/ Factor being investigated	Desmopressin vs. homotoxicological remedies vs. placebo
Comparisons	Comparison is between Desmopressin (dDAVP) (minirin-Valeas) and homotoxicological remedies as well as placebo.
Length of Study/ Follow-up	Up to 3 months.
Outcome measures studied	Number of children who achieved 14 consecutive dry nights.
Results	151 patients were randomised. n=50 to desmopressin, n=50 to homotoxicological remedies and n=51 to receive placebo. Each patient was asked about a familiy history of bladder dysfunction and the number of wet nights per week. Urine analysis, urine culture and ultrasonography of kidney and bladder was conducted. A bladder diary that was completed by the patients or the parents was also used. The first group received desmopressin tablets 0.2mg, once in the evening, plus placebo drops (20 drops three times a day) and the third group received placebo tablets, once in the evening plus placebo drops (20 drops three times a day). Homotoxicological remedies were described as 20 solidago drops three times a day and one biopax tablet in the evening. The treatment was started at different times for each patient, and each one was treated for 3 months.

	Non-responders to the therapy after the first 3 months period were withdrawn from the study. Number of children who achieved 14 consecutive dry nights: In the homotoxicological remedies group 10 out of 50 children achieved 14 consecutive dry nights compared to 26 out of 50 in the desmopressin group and 0 out of 51 in the placebo group.
Safety and adverse effects	No adverse effects were reported.
Does the study answer the question?	Study showed desmopressin is more effective than homotoxicological remedies and placebo. Homotoxicological remedies were more effective than placebo.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Children had a mean age of 8.5 years
Internal Validity	Unclear allocation concealment and blinding

Leboeuf C;Brown P;Herman A;Leembruggen K;Walton D;Crisp TC;

Chiropractic care of children with nocturnal enuresis: a prospective outcome study.[see comment]

Ref ID 386 1991

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	171 in total: n= 71 in no treatment and n=100 in chiropractic treatment.
Inclusion/Exclusion Criteria	Inclusion: wet at least 1 night a week. Exclusion: daytime wetting or soiling at any time; anatomical \physiological abnormalities; recurrent urinary tract infections; infrequent wetting (less than one wet night per week; possible or definite contraindications to spinal manipulative therapy; absence of indication for spinal manipulative therapy as determined by the examining chiropractor.
Patient Characteristics	120 were male, the mean age was 8.3 years. Baseline wetting in the no treatment group was 5.5 days per week and 7 per week, in the chiropractic group.
Recruitment	Press advertisement and primary schools.
Setting	Australia.
Interventions/ Test/ Factor being investigated	Chiropractic treatment.
Comparisons	No treatment.
Length of Study/ Follow-up	2 weeks.
Outcome measures studied	Mean number of wet nights per week at the end of treatment.
Results	2 weeks of treatment, results from Cochrane review. Chiropractic treatment was described as adjustments of the aberrant spinal movement through observation and palpation each visit. The mean number of wet nights per week at the end of treatment:

	In the chiropractic group the mean number of wet nights was 5 per week at the end of treatment compared to 5.5 in the no treatment group.
Safety and adverse effects	1 had headache and stiff neck and 1 had acute pain in lumbar spine.
Does the study answer the question?	The trial showed children who had no treatment had 0.5 fewer wet nights per week at the end of treatment compared to children treated with chiropractic treatment. The study did not give standard deviation values and therefore the mean difference and CI are not estimable.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Children had a mean age of 8.3 years.
Internal Validity	Unclear allocation concealment and blinding

Mao XS;

Acupuncture for primary nocturnal enuresis in children: a randomised clinical trial

Ref ID 1430 1998

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	111 in total: 56 in acupuncture group, 55 in sham acupuncture group.
Inclusion/Exclusion Criteria	Inclusion: age over 5 years, primary nocturnal enuresis diagnosed by 'Chinese Disease Diagnostic and Therapeutic Standards (1994)', normal urine examination, microscopy, pelvic X-ray, and EEG.
Patient Characteristics	The age range was 5 to 15 years, and 79 out of 111 were male.
Recruitment	Not reported.
Setting	Outpatient department.
Interventions/ Test/ Factor being investigated	Group A: acupuncture; Group B: sham acupuncture
Comparisons	Between groups
Length of Study/ Follow-up	None.
Outcome measures studied	The number of children who achieved 14 consecutive dry nights and the number of children who failed to achieve 14 consecutive dry nights or relapsed after treatment.
Results	Treatment length depended upon response Acupuncture was described as a needle being buried under the skin for 3 days and then a new needle buried at the same point for 3 days; children receiving sham acupuncture had a needle placed on the skin for 30 minutes daily for 6 days. The number of children who achieved 14 consecutive dry nights: The number of children who achieved 14 consecutive dry nights in the acupuncture group was 30 out of 56 compared to 17 out of 55 in the sham acupuncture group. The number of children who failed to achieve 14 consecutive dry nights or relapsed after treatment: The number of children who failed to achieve 14 consecutive dry nights or relapsed

	after treatment in the acupuncture group was 26 out of 56 compared to 38 out of 55 in the sham acupuncture group.
Safety and adverse effects	None reported
Does the study answer the question?	The trial showed children treated with acupuncture were more likely to achieve 14 consecutive dry nights compared to children treated with sham acupuncture; children treated with sham acupuncture were more likely to fail to achieve 14 consecutive dry nights or relapse after treatment compared to children treated with acupuncture.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had an age range of 5 to 15 years.
Internal Validity	Unclear allocation concealment and blinding

Radmayr C;Schlager A;Studen M;Bartsch G;

Prospective randomized trial using laser acupuncture versus desmopressin in the treatment of nocturnal enuresis

Ref ID 182 2001

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	40 in total, 20 in each group
Inclusion/Exclusion Criteria	Inclusion: primary monosyptomatic NE, polyuria, over 5 years old, no UTI.
Patient Characteristics	31 were male, the mean age in the desmopressin group was 8.6 years, the mean age in the laser acupuncture group was 8 years. The mean baseline wetting in the desmopressin group was 5.5 wet nights per week and 6 wet nights per week in the laser acupuncture group, the over all rate was 5.5 wet nights per week.
Recruitment	Not reported
Setting	Austria
Interventions/ Test/ Factor being investigated	Group A: desmopressin: Group B: laser acupuncture
Comparisons	Between groups
Length of Study/ Follow-up	6 months after the end of treatment.
Outcome measures studied	The number of children who achieved greater than 90% improvement in the number of dry nights, the number of children who achieved 50% to 90% improvement in the number of dry nights.
Results	Laser acupuncture was described as predefined acupuncture points being stimulated for 30 seconds each at each visit, children had 3 sessions a week and had between 10 and 15 sessions in total; children receiving desmopressin had 20 micrograms intranasal desmopressin, which was increased to 40 micrograms if needed. The number of children who achieved greater than 90% improvement in the number of dry nights: In the desmopressin group 15 out of 20 children achieved a greater than 90% improvement in the number of dry nights compared to 13 out of 20 in the laser acupuncture group.

	The number of children who achieved 50% to 90% improvement in the number of dry nights: In the desmopressin group 2 out of 20 children achieved a 50% to 90% improvement in the number of dry nights compared to 2 out of 20 in the laser acupuncture group.
Safety and adverse effects	None reported
Does the study answer the question?	The trial showed there was no statistically significant difference in the number of children who achieved greater than 90% improvement in the number of dry nights and there was no difference in the number of children who achieved 50% to 90% improvement in the number of dry nights between children treated with laser acupuncture and children treated with desmopressin.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies
Directly applicable to guideline population?	Children in the desmopressin group had a mean age of 8.6 years and children in laser acupuncture group had a mean age of 8 years.
Internal Validity	Unclear allocation concealment and blinding

Reed WR;Beavers S;Reddy SK;Kern G;

Chiropractic management of primary nocturnal enuresis.[see comment]

Ref ID 337 1994

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant	57 in total;11 in control group and 36 in treatment group.
Inclusion/Exclusion Criteria	Inclusion: not daytime wetting, and wet at least 1 night a week. Exclusion: diurnal enuresis, recurrent UTIs, physical abnormalities, urological surgery, contraindication to spinal adjustment, or previous NE treatment or spinal adjustment / chiropractic treatment in previous 4 weeks.
Patient Characteristics	The mean age in the chiropractic group was 8.1 (sd 2.8) years and in the sham group was 8.7 (sd 2.8) years. The mean baseline wetting in the chiropractic group was 9.1 (sd3.15) wet nights per 2 weeks and in the sham group was 11.1 (sd 3).
Recruitment	Advertisment in press.
Setting	Community.
Interventions/ Test/ Factor being investigated	Group A: chiropractic treatment Group B: sham chiropractic treatment
Comparisons	Between groups
Length of Study/ Follow-up	2 weeks
Outcome measures studied	The number of children who achieved greater than 50% improvement in the number of dry nights,and the mean number of wet nights per 2 weeks at follow up.
Results	18 weeks of treatment Chiropractic treatment was described as patients having spinal subluxation through high velocity, short lever thrust every 10 days. Children were evaluated for segmental dysfunction using observation and palpation. Children receiving sham chiropractic treatment followed the same procedure but received sham adjustment.

	The number of children who achieved greater than 50% improvement in the number of dry nights: In the chiropractic group 8 out of 31 children had a greater than 50% improvement in the number of dry nights compared to 0 out of 15 in the sham group. The mean number of wet nights per 2 weeks at follow up: In the chiropractic group the mean number of wet nights per 2 weeks at follow up was 7.6 (sd 4.3) compared to 11.2 (sd 3.5) in the sham group.
Safety and adverse effects	None reported.
Does the study answer the question?	The trial showed there was no statistically significant difference in the number of children who achieved greater than 50% improvement in the number of dry nights between children treated with chiropractic treatment and children treated with sham chiropractic treatment. The study showed children treated with chiropractic treatment had fewer wet nights per 2 weeks at follow up compared to children treated with sham chiropractic treatment.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had a mean age of 8.1 to 8.7 years.
Internal Validity	Unclear allocation concealment and blinding

Grading: 2-	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

Bjorkstrom G;Hellstrom AL;Andersson S;

Electro-acupuncture in the treatment of children with monosymptomatic nocturnal enuresis

Ref ID 634 2000

Study Type Cohort **Funding** Not reported

Number of participant	25 children with monosymptomatic nocturnal enuresis and treated earlier without success.
Inclusion/Exclusion Criteria	Inclusion: monosymptomatic NE and treated earlier without success.
Patient Characteristics	Children had an age range of 7 to 16 years and the baseline median wetting was 4.7 nights per week.
Recruitment	Not reported.
Setting	Sweden
Interventions/ Test/ Factor being investigated	Electro-acupuncture.
Comparisons	None.
Length of Study/ Follow-up	6 months.
Outcome measures studied	The mean number of dry nights at follow up, 90% reduction in wet nights, 50 to 90% reduction in the mean number of wet nights.
Results	Twenty 30 minute sessions of electro-acupuncture over 8 weeks of treatment. Electro-acupuncture was described as follows: the child placed in a supine relaxed position, and 7 disposable needles placed at specific points. For the first 3 sessions these were manually stimulated. After this 2 pairs of needles were connected to an electro-stimulator. The study showed the mean number of dry nights increased to 3.5 (from 2.3) during the last 3 weeks of treatment, at 3 month follow up the mean number of dry nights was 4.3 and at 6 month follow up the mean number of dry nights was 5. At the end of treatment (6 months) 8% of patients achieved a 90% reduction in number of wet nights, and at 3 and 6 months 22% had achieved a 90% reduction number of wet nights. At 6 months 26% had achieved a 50% to 90% reduction in number of wet nights. 1 child dropped out due to a fear of needles.
Safety and adverse effects	None reported
Does the study answer the question?	The study showed children treated with electro-acupuncture can become dry.
Effect due to factor in study?	Yes
Consistency of results with other studies?	No other similar studies.
Directly applicable to guideline population?	Children had an age range of 7 to 16 years.

Internal Validity Well covered

Question: What is the clinical and cost effectiveness of dose escalation in desmopressin (nasal, tablets and melts) for children and young people under 19 years old who have nocturnal enuresis?

Grading: 1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Schulman SL;Stokes A;Salzman PM;

The efficacy and safety of oral desmopressin in children with primary nocturnal enuresis

Ref ID 176 2001

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant	193 in total; of the 187 patients who completed the dose ranging phase of the study (phase 1), 148 continued into the dose titration phase (trial 2).
Inclusion/Exclusion Criteria	Inclusion: at least 3 wet nights a week, informed consent, no treatment in previous 30 days, aged 6-16 years, children who had not responded to dosemoressin in a first trial of desmopressin Exclusion: organic causes of NE, day time wetting, organic urological disease, diabetes insipidus, UTI, known hypersensitivity to desmopressin, antibiotics, diuretics, hyperactivity
Patient Characteristics	In trial one the patient characteristics were 133 out of 193 were male, mean baseline wetting in 2 weeks in group 1, was 11 (range 5-14), in group 2, 10 (range 4-14), in group 3, 10 (range 6-14), in group 4, 10 (range 6-14), of these 148 continued to this trial
Recruitment	Not reported
Setting	16 centres in USA
Interventions/ Test/ Factor being investigated	Group A: 0.2 mg oral desmopressin increased every 2 weeks if no response Group B: matching placebo, tablets changed every 2 weeks if no response
Comparisons	Between treatment groups
Length of Study/ Follow-up	No follow up, 8 weeks of treatment
Outcome measures studied	Number of children who required maximum increase in dose, number of children who required 0.2 mg, 0.4mg desmopressin, improvement of 50% or more from baseline wetting, mean number of wet nights in first and last 2 weeks, drop out, adverse events
Results	Number of children who required maximum increase in dose by 8 weeks (dose titration phase): In group E (desmopressin) 86 out of 99 needed the maximum increase (0.6mg) and 38 out of 38 in group F (placebo) had beem titrated to the maximum dose. Number of children who required 0.2mg desmopressin s: In group E (desmopressin) 1 out of 99 needed 0.2mg desmopressin and 0 out of 38 in group F (placebo) Number of children who required an increase to 0.4 mg desmopressin: In group E (desmopressin) 12 out of 99 needed an increase to 0.4 mg desmopressin and 0 out of 38 in group F (placebo) Improvement of 50% or more from baseline wetting: In group E (desmopressin) 51 out of 99 (28 on 0.2 mg, 16 on 0.4 mg, 8 on 0.6 mg) improved compared to 7 out of 35 in group F (placebo) Mean number of wet nights in first 2 weeks (0.2mg desmopressin): In group E (desmopressin 109 patients) the mean number of wet nights was 4 (SD 1.57) and in group F (placebo 38 patients) the mean number of wet nights was 5 (SD 1.54) Mean number of wet nights per week in last 2 weeks of treatment (up to 0.6 mg desmopressin):

	In group E (desmopressin 99 patients) the mean number of wet nights was 3.2 (SD 1.69) and in group F (placebo 38 patients) was 4.5 (SD 1.5) Drop outs: 11 dropped out of group E (desmopressin), 0 dropped out of group F (placebo) 1 child on desmopressin and 1 on placebo stopped before end of trial because of nervousness Adverse events (1 or more per child): 43 out of 143 on desmopressin and 13 out of 48 on placebo - rhinitis, pharyngitis, infection, headache and fever Authors reported most were unrelated to treatment and were resolved by end of trial
Safety and adverse effects	rhinitis, pharyngitis, infection, headache and fever Authors reported most were unrelated to treatment and were resolved by end of trial
Does the study answer the question?	The study showed in this popultation where children had failed to achieve dryness in a previous study; most children required the full dose increase of desmopressin.
Effect due to factor in study?	Yes, alhtough all chidlren had previously failed desmopressin treatment
Consistency of results with other studies?	No other studies
Directly applicable to guideline population?	Children had failed to respond to desmopressin
Internal Validity	

Grading: 2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

Matthiesen TB;Rittig S;Djurhuus JC;Norgaard JP;

A dose titration, and an open 6-week efficacy and safety study of desmopressin tablets in the management of nocturnal enuresis

Ref ID 1052 1994

Study Type	Cohort	**Funding**	Ferring AB, Sweden provided desmopressin tablets.

Number of participant	33 patients
Inclusion/Exclusion Criteria	Inclusion: 3 or more wet nights per week during a 2 week observation period, normal on physical examination, normal hematocrit, serum creatine, serum sodium serum potassium and serum albumin levels, sterile urine, no evidence of any other urological disease, and no treatment in previous 3 weeks.
Patient Characteristics	20 out of 33 were male. The mean age was 11.6 (sd 3) years and the age range was 7 to 18 years. All children except 9 had previously been treated for NE.
Recruitment	Not reported
Setting	Denmark
Interventions/ Test/ Factor being investigated	Dose escalation of tablet desmopressin.
Comparisons	No comparison.
Length of Study/ Follow-up	2 weeks of treatment.
Outcome measures studied	Number of children who became dry, number of children who dropped out.
Results	The study conducted a 2 week dose titration period. During this period children were asked to keep a diary and were seen every 2 weeks. The patients received 200 micrograms tablet desmopressin 1 hour before bed for 1 week. If after the patient was not dry for the whole week the dose was increased to 400 micrograms tablet desmopressin for one week. Number of children who became dry (no wet nights for whole week while on treatment): 5 children out of 33 became dry while treated with 200 micrograms desmopressin for 1 week. 26 children then had their dosage increased to 400 micrograms tablet desmopressin for 1 week and during this time 2 children became dry. Number of children who dropped out: During the week where children were given 200 micrograms desmopressin 2 children dropped out. During the following week where children were given 400 micrograms desmopressin another 2 children dropped out.
Safety and adverse effects	None reported
Does the study answer the question?	The study shows children treated with desmopressin can become dry if they have their dosage increased after not responding to the first dose.
Effect due to factor in study?	Yes

Consistency of results with other studies?	No other studies.
Directly applicable to guideline population?	Children had a mean age of 11.6 (sd 3) years.
Internal Validity	Poorly addressed