

Nocturnal enuresis

The management of bedwetting in children and young people

Clinical guideline

Methods, evidence and recommendations

October 2010 Final

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Clinical Excellence*

NOCTURNAL ENURESIS: the management of bedwetting in children and young people – FINAL VERSION

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Preface

(to be added for final document)

Patient-Centered Care

This guideline offers best practice advice on the care of children and young people with bedwetting.

Treatment and care should take into account patients' needs and preferences. Children and young people with bedwetting and their parents and/or carers should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If a child or young person is not old enough or does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from www.wales.nhs.uk/consent).

If the patient is under 16, healthcare professionals should follow the guidelines in 'Seeking consent: working with children' (available from www.dh.gov.uk/consent).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

Families and carers should have the opportunity to be involved in decisions about treatment and care. Where appropriate, for example for older children, this should be with the child's agreement.

Families and carers should also be given the information and support they need.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in 'Transition: getting it right for young people' (available from www.dh.gov.uk).

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with bedwetting. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Key priorities for implementation

- Inform children with bedwetting and their parents or carers that bedwetting is not the child's fault and that punitive measures should not be used in the management of bedwetting. **[1.1.1]**
- Offer support, assessment and treatment to all children with bedwetting and their parents or carers, tailored to the child's and parents' or carers' circumstances and needs. **[1.1.2]**
- Do not exclude younger children (for example, those under 7 years) from the management of bedwetting on the basis of age alone. **[1.1.3]**
- Discuss with the child's parents or carers whether they need support, particularly if they are having difficulty coping with the burden of bedwetting, or if they are expressing anger, negativity or blame towards the child. **[1.3.17]**
- Consider whether or not it is appropriate to offer alarm or drug treatment, depending on the age of child, the frequency of bedwetting and the motivation and needs of the child and family. **[1.4.5]**
- Address excessive or insufficient fluid intake or abnormal toileting patterns before starting other treatments for bedwetting in children. **[1.5.6]**
- Explain to children and parents or carers that reward systems with positive rewards for agreed behaviour rather than dry nights should be used either alone or in conjunction with other treatments for bedwetting. For example, rewards may be given for :
 - drinking recommended levels of fluid during the day
 - using the toilet to pass urine before sleep
 - engaging in management (for example, taking medication or helping to change sheets). **[1.7.1]**
- Offer an alarm as the first-line treatment to children with bedwetting, unless
 - an alarm is considered undesirable to the child or parents and carers
 - or**
 - an alarm is considered inappropriate, particularly if:
 - the child has very infrequent bedwetting (that is, less than 1–2 wet beds per week)

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- the parents or carers are having emotional difficulty coping with the burden of bedwetting
 - the parents or carers are expressing anger, negativity or blame towards the child.**[1.8.1]**
- Offer desmopressin to children with bedwetting if:
 - rapid onset and/or short-term improvement in bedwetting is the priority of treatment **or**
 - an alarm is inappropriate or undesirable.**[1.10.1]**
- Refer children with bedwetting that has not responded to courses of treatment with an alarm and/or desmopressin for further review and assessment of factors that may be associated with a poor response, such as an overactive bladder, an underlying disease or social and emotional factors. **[1.11.6]**

1 Guidance

The following guidance is based on the best available evidence. These recommendations apply to all healthcare professionals who are involved in the management of bedwetting in children and young people. Healthcare professionals are reminded of their duty under the Disability Discrimination Act (2005) to make reasonable adjustments to ensure that all people have the same opportunity for health.

For the purposes of this guideline we have used the terms 'bedwetting' and 'daytime symptoms' to describe those symptoms that may be experienced by the population who present for treatment of 'bedwetting'. The term 'child' is used throughout to signify child or young person under 19 years, unless otherwise stated.

The following definitions were used for this guideline:

- **Bedwetting:** involuntary wetting during sleep without any inherent suggestion of frequency or pathophysiology.
- **Daytime symptoms:** daytime urinary symptoms such as wetting, frequency or urgency.
- **'Response to an intervention:'** the child has achieved 14 consecutive dry nights or a 90% improvement in the number of wet nights per week.
- **'Partial response:'** the child's symptoms have improved but 14 consecutive dry nights or a 90% improvement in the number of wet nights per week has not been achieved.

1.1 *Principles of care*

- 1.1.1** Inform children with bedwetting and their parents or carers that bedwetting is not the child's fault and that punitive measures should not be used in the management of bedwetting.
- 1.1.2** Offer support, assessment and treatment to all children with bedwetting and their parents or carers, tailored to the child's and parents' or carers' circumstances and needs.
- 1.1.3** Do not exclude younger children (for example, those under 7 years) from the management of bedwetting on the basis of age alone.
- 1.1.4** Perform regular medication reviews for children on repeated courses of drug treatment for bedwetting.

1.2 *Information for the child and family*

- 1.2.1** Offer information, tailored to the child's needs, to children being treated for bedwetting and their parents or carers.
- 1.2.2** Offer information and details of support groups to children being treated for bedwetting and their parents or carers.
- 1.2.3** Offer information about practical ways to reduce the impact of bedwetting before and during treatment (for example, using bed protection and washable and disposable products).

1.3 *Assessment and investigation*

- 1.3.1** Ask whether the bedwetting started in the last few days or weeks. If so, consider whether this is a presentation of a systemic illness.
- 1.3.2** Ask if the child had previously been dry at night without assistance for 6 months. If so, enquire about any possible medical, emotional or physical triggers, and consider whether assessment and treatment is needed for any identified triggers.
- 1.3.3** Ask about the pattern of bedwetting, including questions such as:
 - How many nights a week does bedwetting occur?
 - How many times a night does bedwetting occur?
 - Does there seem to be a large amount of urine?

- At what times of night does the bedwetting occur?
- Does the child wake up after bedwetting?

1.3.4 Ask about the presence of daytime symptoms in a child with bedwetting, including:

- daytime frequency (that is, passing urine more than seven times a day)
- daytime urgency
- daytime wetting
- passing urine infrequently (fewer than four times a day)
- abdominal straining or poor urinary stream
- pain passing urine.

1.3.5 Ask about daytime toileting patterns in a child with bedwetting, including:

- whether daytime symptoms occur only in some situations
- avoidance of toilets at school or other settings
- whether the child goes to the toilet more or less frequently than his or her peers.

1.3.6 Ask about the child's fluid intake throughout the day. In particular, ask whether the child or the parents or carers are restricting fluids.

1.3.7 Consider whether a record of the child's fluid intake, daytime symptoms, bedwetting and toileting patterns would be useful in the assessment and management of bedwetting. If so, consider asking the child and parents or carers to record this information.

1.3.8 Do not perform urinalysis routinely in children with bedwetting, unless any of the following apply:

- bedwetting started in the last few days or weeks
- the child has daytime symptoms
- the child has any signs of ill health

- there is a history, symptoms or signs suggestive of urinary tract infections
- there is a history, symptoms or signs suggestive of diabetes mellitus.

1.3.9 Assess whether the child has any comorbidities or there are other factors to consider, in particular:

- constipation and/or soiling
- developmental, attention or learning difficulties
- diabetes mellitus
- behavioural or emotional problems
- family problems or vulnerable child or family.

1.3.10 Consider assessment, investigation and/or referral when bedwetting is associated with:

- severe daytime symptoms
- a history of recurrent urinary infections
- known or suspected physical or neurological problems
- comorbidities or other factors (for example, those listed in recommendation 1.3.9).

1.3.11 Investigate and treat children with suspected urinary tract infection in line with 'Urinary tract infection' (NICE clinical guideline 54).

1.3.12 Investigate and treat children with soiling or constipation in line with 'Constipation in children and young people' (NICE clinical guideline 99).

1.3.13 Children and young people with suspected type 1 diabetes should be offered immediate (same day) referral to a multidisciplinary paediatric diabetes care team that has the competencies needed to confirm diagnosis and to provide immediate care

[This recommendation is from 'Type 1 diabetes' (NICE clinical guideline 15).

- 1.3.14** Consider investigating and treating daytime symptoms before bedwetting if daytime symptoms predominate.
- 1.3.15** Consider involving a professional with psychological expertise for children with bedwetting and emotional or behavioural problems.
- 1.3.16** Discuss factors that might affect treatment and support needs, such as:
- the child's sleeping arrangements (for example, does the child have his or her own bed or bedroom)
 - the impact of bedwetting on the child and family
 - whether the child and parents or carers have the necessary level of commitment, including time available, to engage in a treatment programme.
- 1.3.17** Discuss with the child's parents or carers whether they need support, particularly if they are having difficulty coping with the burden of bedwetting, or if they are expressing anger, negativity or blame towards the child.
- 1.3.18** Consider child maltreatment¹ if:
- a child is reported to be deliberately bedwetting
 - parents or carers are seen or reported to punish a child for bedwetting despite professional advice that the symptom is involuntary
 - a child has secondary daytime wetting or secondary bedwetting that persists despite adequate assessment and management unless there is a medical explanation (for example, urinary tract infection) or clearly identified stressful situation that is not part of maltreatment (for example, bereavement, parental separation).

[This recommendation is adapted from 'When to suspect child maltreatment' (NICE clinical guideline 89).]

¹ For the purposes of the child maltreatment guideline, to consider child maltreatment means that maltreatment is one possible explanation for the alerting feature or is included in the differential diagnosis.

1.3.19 Use the findings of the history to inform the diagnosis (according to table 1) and management of bedwetting.

Table 1 Findings from the history and their possible interpretation

Findings from history	Possible interpretation
Large volume of urine in the first few hours of night	Typical pattern for bedwetting only.
Variable volume of urine, often more than once a night	Typical pattern for children who have bedwetting and daytime symptoms with possible underlying overactive bladder.
Bedwetting every night	Severe bedwetting, which is less likely to resolve spontaneously than infrequent bedwetting.
Previously dry for more than 6 months	Bedwetting is defined as secondary.
<ul style="list-style-type: none"> •Daytime frequency •Daytime urgency •Daytime wetting •Abdominal straining or poor urinary stream •Pain passing urine 	Any of these may indicate the presence of a bladder disorder such as overactive bladder or more rarely (when symptoms are very severe and persistent) an underlying urological disease.
Constipation	A common comorbidity that can cause bedwetting and requires treatment (see 'Constipation in children and young people' [NICE clinical guideline 99]).
Soiling	Frequent soiling is usually secondary to underlying faecal impaction and constipation which may have been unrecognised.
Inadequate fluid intake	May mask an underlying bladder problem, such as overactive bladder disorder, and may impede the development of an adequate bladder capacity.
Behavioural and emotional problems	These may be a cause or a consequence of bedwetting. Treatment may need to be tailored to the specific requirements to each child and family.
Family problems	A difficult or 'stressful' environment may be a trigger for bedwetting. These factors should be addressed alongside the management of bedwetting.
Practical issues	Easy access to a toilet at night, sharing a bedroom or bed and proximity of parents to provide support are all important issues to consider and address when considering treatment, especially with an alarm.

1.4 Planning management

- 1.4.1** Explain the condition, the effect and aims of treatment, and the pros and cons of the proposed treatment to the child and parents or carers.
- 1.4.2** Clarify what the child and parents or carers hope the treatment will achieve. Ask whether short-term dryness is a priority for family or recreational reasons (for example, for a sleep-over).
- 1.4.3** Explore the child's views about their bedwetting, including:
- what the child thinks the main problem is
 - whether the child thinks the problem needs treatment.
- 1.4.4** Explore and assess the ability of the family to cope with using an alarm for the treatment of bedwetting.
- 1.4.5** Consider whether or not it is appropriate to offer alarm or drug treatment, depending on the age of child, the frequency of bedwetting and the motivation and needs of the child and family.

1.5 Advice on fluid intake, diet and toileting patterns

- 1.5.1** Advise children with bedwetting and their parents or carers that:
- adequate daily fluid intake is important in the management of bedwetting
 - daily fluid intake varies according to ambient temperature, dietary intake and physical activity. A suggested intake of drinks is given in table 2:

Table 2 Suggested daily intake of drinks for children and young people

Age	Sex	Total drinks per day
4–8 years	Female	1000–1400 ml
	Male	1000–1400 ml
9–13 years	Female	1200–2100 ml
	Male	1400–2300 ml
14–18 years	Female	1400–2500 ml
	Male	2100–3200 ml

- 1.5.2 Advise the child and parents or carers that the consumption of caffeine-based drinks should be avoided in children with bedwetting.
- 1.5.3 Advise the child and parents or carers to eat a healthy diet and not to restrict diet as a form of treatment for bedwetting in children.
- 1.5.4 Advise the child of the importance of using the toilet at regular intervals throughout the day.
- 1.5.5 Advise parents or carers to encourage the child to use the toilet to pass urine at regular intervals during the day and before sleep (typically between four and seven times in total). This should be continued alongside the chosen treatment for bedwetting.
- 1.5.6 Address excessive or insufficient fluid intake or abnormal toileting patterns before starting other treatment for bedwetting in children.
- 1.5.7 Suggest a trial without nappies or pull-ups for a child with bedwetting who is toilet trained by day and is wearing nappies or pull-ups at night.

1.6 *Lifting and waking*

- 1.6.1 Offer advice on waking and lifting during the night as follows:
 - Neither waking nor lifting children with bedwetting, at regular times or randomly, will promote long-term dryness.
 - Waking by parents or carers, either at regular times or randomly, should be used only as a practical measure in the short-term management of bedwetting.
 - Young people with bedwetting that has not responded to treatment may find self-instigated waking a useful management strategy.

1.7 *Reward systems*

- 1.7.1 Explain to children and parents or carers that reward systems with positive rewards for agreed behaviour rather than dry nights should be used either alone or in conjunction with other treatments for bedwetting. For example, rewards may be given for:
 - drinking recommended levels of fluid during the day
 - using the toilet to pass urine before sleep

- engaging in management (for example, taking medication or helping to change sheets).

1.7.2 Inform parents or carers that they should not use systems that penalise or remove previously gained rewards.

1.7.3 Advise parents or carers to use reward systems alone for the initial treatment of bedwetting in young children who have some dry nights.

1.8 *Initial treatment – alarms*

1.8.1 Offer an alarm as the first-line treatment to children with bedwetting, unless:

- an alarm is considered undesirable to the child or parents and carers
or
- an alarm is considered inappropriate, particularly if:
- the child has very infrequent bedwetting (that is, less than 1–2 wet beds per week)
- the parents or carers are having emotional difficulty coping with the burden of bedwetting
- the parents or carers are expressing anger, negativity or blame towards the child.

1.8.2 Assess the response to an alarm by 4 weeks and continue with treatment if the child is showing early signs of response². Stop treatment only if there are no early signs of response.

1.8.3 Continue alarm treatment in children with bedwetting who are showing signs of response until a minimum of 2 weeks' uninterrupted dry nights has been achieved.

1.8.4 Assess whether it is appropriate to continue with alarm treatment if complete dryness is not achieved after 3 months. Only continue with alarm treatment if the child's bedwetting is still improving and the child and parents or carers are motivated to continue.

² Early signs of a response may include smaller wet patches, waking to the alarm, the alarm going off later and fewer times per night and fewer wet nights.

- 1.8.5** Do not exclude alarm treatment as an option for bedwetting in children with:
- daytime symptoms as well as bedwetting
 - secondary bedwetting.
- 1.8.6** Consider an alternative type of alarm (for example, a vibrating alarm) for the treatment of bedwetting in children who have a hearing impairment.
- 1.8.7** Consider an alarm for the treatment of bedwetting in children with learning difficulties and/or physical disabilities. Tailor the type of alarm to each child's needs and abilities.
- 1.8.8** Consider an alarm for the treatment of bedwetting in children under 7 years, depending on their ability, maturity, motivation and understanding of the alarm.

Using an alarm

- 1.8.9** Inform parents or carers about the benefits of alarms combined with reward systems. Advise them to use positive rewards for desired behaviour, such as waking up when the alarm goes off, going to the toilet after the alarm has gone off, returning to bed and resetting the alarm.
- 1.8.10** Encourage children with bedwetting and their parents or carers to discuss and agree on their roles and responsibilities for using the alarm and the use of rewards.
- 1.8.11** Ensure that advice and support are available to children and parents or carers who are given an alarm, and agree how these should be obtained. Be aware that they may need a considerable amount of help in learning how to use an alarm.
- 1.8.12** Inform the child and parents or carers that the aims of alarm treatment for bedwetting are to train the child to:
- recognise the need to pass urine
 - wake to go to the toilet or hold on
 - learn over time to hold on or to wake spontaneously and stop wetting the bed.
- 1.8.13** Inform the child and parents or carers that:
- alarms have a high long-term success rate

- using an alarm can disrupt sleep
- that parents or carers may need to help the child to wake to the alarm
- using an alarm requires sustained parental and child commitment, involvement and effort
- they will need to record their progress (for example, if and when the child wakes and how wet the child and bed are)
- alarms are not suitable for all children and families.

1.8.14 If offering an alarm for bedwetting in children, inform the child and parents or carers how to:

- set and use the alarm
- respond to the alarm when it goes off
- maintain the alarm
- deal with problems with the alarm, including who to contact when there is a problem
- return the alarm when they no longer need it.

1.8.15 Inform the child and parents or carers that it may take a few weeks for the early signs of a response to the alarm to occur and that these may include:

- smaller wet patches
- waking to the alarm
- the alarm going off later and fewer times per night
- fewer wet nights.

1.8.16 Inform the child and parents or carers that dry nights may be a late sign of response to the alarm and may take weeks to achieve.

1.8.17 Inform the parents or carers that they can restart using the alarm immediately, without consulting a healthcare professional, if the child starts bedwetting again following response to alarm treatment.

1.9 *Lack of response to alarm treatment*

- 1.9.1** If bedwetting does not respond to initial alarm treatment, offer:
- combination treatment with an alarm and desmopressin **or**
 - desmopressin alone if continued use of alarm is no longer acceptable to the child or parents and carers.
- 1.9.2** Offer desmopressin alone to children with bedwetting if there has been a partial response to a combination of an alarm and desmopressin following initial treatment with an alarm.

1.10 Initial treatment – desmopressin

- 1.10.1** Offer desmopressin to children with bedwetting if:
- rapid-onset and/or short-term improvement in bedwetting is the priority of treatment **or**
 - an alarm is inappropriate or undesirable.
- 1.10.2** Do not exclude desmopressin as an option for the management of bedwetting in children who also have daytime symptoms. However, do not use desmopressin in the treatment of children who only have daytime wetting.
- 1.10.3** In children who have failed to achieve complete dryness after 1 to 2 weeks of the initial dose of desmopressin (200 micrograms for Desmotabs and 120 micrograms for DesmoMelt), consider increasing the dose (to 400 micrograms of Desmotabs and 240 micrograms of DesmoMelt).
- 1.10.4** Assess the response to desmopressin at 4 weeks and continue treatment for 3 months if there are signs of a response. Consider stopping if there are no signs of response. Signs of response include:
- smaller wet patches
 - fewer wetting episodes per night
 - fewer wet nights.
- 1.10.5** Consider desmopressin for children between 5 and 7 years if treatment is required and an alarm is inappropriate or undesirable.
- 1.10.6** Do not exclude desmopressin as an option for the treatment of bedwetting in children with sickle cell disease if an alarm is inappropriate or undesirable and they can comply with night-time fluid restriction. Provide advice about withdrawal of desmopressin at times of sickle cell crisis.
- 1.10.7** Do not exclude desmopressin as an option for the treatment of bedwetting in children with emotional, attention or behavioural problems or developmental and learning difficulties if an alarm is inappropriate or undesirable and they can comply with night-time fluid restriction.
- 1.10.8** Do not routinely measure weight, serum electrolytes, blood pressure and urine osmolality in children being treated with desmopressin for bedwetting.

- 1.10.9** If offering desmopressin for bedwetting in children, inform the child and parents or carers:
- that many children, but not all, will experience a reduction in wetness
 - how desmopressin works
 - of the importance of fluid restriction from 1 hour before until 8 hours after taking desmopressin
 - that it should be taken at bedtime
 - if appropriate, how to increase the dose if there is an inadequate response to the starting dose
 - that many children, but not all, will relapse when treatment is withdrawn
 - to continue treatment with desmopressin for 3 months
 - that repeated courses of desmopressin can be used.
- 1.10.10** Consider advising that desmopressin should be taken 1–2 hours before bedtime in children with bedwetting that has either partially responded or not responded to desmopressin taken at bedtime. Ensure that the child can comply with fluid restriction starting from 1 hour before the drug is taken.
- 1.10.11** Consider continuing treatment with desmopressin for children with bedwetting that has partially responded, as bedwetting may improve for up to 6 months after starting treatment.

1.11 *Children experiencing recurrence of bedwetting*

- 1.11.1** Consider alarm treatment again if a child who was previously dry with an alarm has started regularly bedwetting again.
- 1.11.2** Offer combination treatment with an alarm and desmopressin to children who have more than one recurrence of bedwetting following successful treatment with an alarm.
- 1.11.3** Consider using repeated courses of desmopressin for children with bedwetting that has responded to desmopressin treatment but who

experience repeated recurrences. Withdraw desmopressin treatment at regular intervals (for 1 week every 3 months) to check if dryness has been achieved when using it for the long-term treatment of bedwetting.

- 1.11.4** Gradually withdraw desmopressin rather than suddenly stopping it if a child has had a recurrence of bedwetting following response to previous treatment courses.
- 1.11.5** Consider alarm treatment as an alternative to restarting desmopressin for children who have repeated recurrences of bedwetting after successful treatment with desmopressin, if an alarm is now considered appropriate and desirable.

Lack of response to initial treatment options

- 1.11.6** Refer children with bedwetting that has not responded to courses of treatment with an alarm and/or desmopressin for further review and assessment of factors that may be associated with a poor response, such as an overactive bladder, an underlying disease or social and emotional factors.

1.12 Anticholinergics

The use of anticholinergics for bedwetting in children is discussed in the recommendations in this section. Not all anticholinergics have a UK marketing authorisation for treating bedwetting in children. If a drug without a marketing authorisation for this indication is prescribed, informed consent should be obtained and documented.

- 1.12.1** Do not use an anticholinergic alone for the management of bedwetting in children without daytime symptoms.
- 1.12.2** Consider an anticholinergic combined with desmopressin for bedwetting in children who also have daytime symptoms and have been assessed by a healthcare professional with expertise in the prescribing the combination of an anticholinergic and desmopressin.
- 1.12.3** Consider an anticholinergic combined with desmopressin for children who have been assessed by a healthcare professional with expertise in the management of bedwetting that has not responded to an alarm and/or desmopressin and have any of the following:

- bedwetting that has partially responded to desmopressin alone
- bedwetting that has not responded to desmopressin alone
- bedwetting that has not responded to combination of alarm and desmopressin.

1.12.4 Consider continuing treatment for children with bedwetting that has partially responded to desmopressin combined with an anticholinergic, as bedwetting may continue to improve for up to 6 months after starting treatment.

1.12.5 Consider using repeated courses of desmopressin combined with an anticholinergic in children who have responded to this combination but experience repeated recurrence of bedwetting following previous response to treatment.

1.12.6 If offering an anticholinergic combined with desmopressin for bedwetting in children, inform the child and parents or carers:

- that success rates are difficult to predict, but more children are drier with this combination than with desmopressin alone
- that desmopressin and an anticholinergic can be taken together at the same time before bed
- to continue treatment for 3 months
- that repeated courses can be used.

1.12.7 Do not offer an anticholinergic combined with imipramine for the treatment of bedwetting in children.

1.13 *Tricyclic antidepressants*

1.13.1 Do not use tricyclic antidepressants as a first-line treatment for bedwetting in children.

1.13.2 If offering a tricyclic antidepressant, imipramine³ should be used for the treatment of bedwetting in children.

1.13.3 Consider imipramine for children with bedwetting who:

³ Imipramine is currently not licensed for use in children under the age of 6 years.

- have not responded to all other treatments **and**
- have been assessed by a healthcare professional with expertise in the management of bedwetting that has not responded to an alarm and/or desmopressin.

1.13.4 If offering imipramine for bedwetting in children, inform the child and parents or carers:

- that many children, but not all, will experience a reduction in wetness
- how imipramine works
- that it should be taken before bedtime
- that the dose should be increased gradually
- about relapse rates, (for example, more than two out of three children will relapse after a 3-month course of imipramine)
- that the initial treatment course is for 3 months and further courses may be considered
- about the particular dangers of imipramine overdose, and the importance of taking only the prescribed amount and storing it safely.

1.13.5 Perform a medical review every 3 months in children who are using repeated courses of imipramine for the management of bedwetting.

1.13.6 Withdraw imipramine gradually when stopping treatment for bedwetting in children.

1.14 *Training programmes for the management of bedwetting.*

1.14.1 Do not use strategies that recommend the interruption of urinary stream or encourage infrequent passing of urine during the day.

1.14.2 Do not use dry-bed training⁴ with or without an alarm for the treatment of bedwetting in children.

⁴ A training programme that combines a number of different behavioural interventions that may include rewards, punishment training routines and waking routines and be undertaken with or without an enuresis alarm.

1.15 Children under 5 years with bedwetting

Children are generally expected to be dry by a developmental age of 5 years, and historically it has been common practice not to offer advice to families of children who are younger than 5 years and are bedwetting. This section provides recommendations specific to the under 5 age group indicating situations where healthcare professionals can offer useful advice and interventions.

- 1.15.1** Reassure parents or carers that many children under 5 years wet the bed, for example, approximately one in five children of 4 and a half years wets the bed at least once a week.
- 1.15.2** Ask whether toilet training has been attempted, and if not, ask about the reasons for this and offer support and advice. If there are no reasons why toilet training should not be attempted, advise parents or carers to toilet train their child.
- 1.15.3** Suggest a trial of at least 2 nights in a row without nappies or pull-ups for a child with bedwetting who is under 5 years and has been toilet trained by day for longer than 6 months. Consider a longer trial in children:
- who are older
 - who achieve a reduction in wetness
 - whose family circumstances allow the trial to continue.
- 1.15.4** Advise the parents or carers of child under 5 years with bedwetting that if the child wakes at night, they should take him or her to the toilet.
- 1.15.5** Consider further assessment and investigation to exclude a specific medical problem for children over 2 years who, despite awareness of toileting needs and showing appropriate toileting behaviour, are struggling to not wet themselves during the day as well as the night.
- 1.15.6** Assess children under 5 years with bedwetting for constipation, in line with 'Constipation in children and young people' (NICE clinical guideline 99), as undiagnosed chronic constipation is a common cause of wetting and soiling in younger children.

2 Introduction

2.1 Nocturnal Enuresis and Bedwetting

2.1.1 Impact of Nocturnal Enuresis and Bedwetting

Bedwetting is a widespread and distressing condition that can have a deep impact on the child/young person's behavior and on their emotional and social life^{65,106}. It is also particularly stressful for to the parents or guardians. Butler (1998)²³ has argued that the degree of parental concern and extent of child distress are important in determining the clinical significance of the problem. Bedwetting can affect normal daily routines and social activities such as sleep overs or school trips. It can also generate much more serious feelings and behaviours, such as a sense of helplessness and a lack of hope and optimism¹⁰⁶, feelings of being different from others, feelings of guilt and shame, humiliation, victimization and loss of self-esteem^{22,23}. There is evidence that children with bedwetting have higher than average levels of oppositional behaviour and conduct problems⁷⁷. While the majority of parents do not get angry with their child as a result of bedwetting, there is evidence of a link with child punishment, including physical abuse by parents/guardians¹³³. The correlation between nocturnal enuresis and lower self esteem seems to be a common finding⁶⁵, although the definition of self esteem varies between studies. Boys seem to rate bedwetting as more difficult than girls²⁹ and boys had lower self esteem scores⁶⁵. Collier (2002)³⁶ also reported that girls with NE had significantly higher self esteem scores compared to boys. However, Theunis (2002)¹⁴⁸ reported that enuretic girls had a lower perceived competence concerning their scholastic skills and social acceptance compared to the boys, but it was not clear whether this was the group with the highest percentage of daytime wetting. There was evidence that after successful treatment self esteem scores increased in both boys and girls⁶⁶.

2.1.2 Epidemiology of Nocturnal Enuresis and Bedwetting

The epidemiology of bedwetting is complicated by the variety of definitions used in studies. The prevalence of bedwetting decreases with age. The Avon Longitudinal Study found that infrequent bedwetting (defined in their study as bedwetting less than 2 nights per week) has a prevalence of 21% at 4 years and 6 months and 8% at 9 years and 7 months of age. Nocturnal enuresis (defined in their study as bedwetting more than 2 nights per week) has a prevalence of 8% at 4 years and 6 months and 1.5% at 9 years and 7 months of age²⁰. An epidemiological study in Hong Kong¹⁷² defined bedwetting as ≥ 1 wet night over a 3 month period and reported a

prevalence of 16.1% at age 5 years, 10.1% at 7 years and 2.2% at 19 years. The prevalence is greater for boys than girls at all ages.

2.1.3 Classification and definitions of Nocturnal Enuresis and Bedwetting

The terminology used to describe both lower urinary tract symptoms and associated conditions or syndromes has been the subject of much confusion.

Terms used include nocturnal enuresis, enuresis, bedwetting and incontinence of urine when sleeping.

The Diagnostic & Statistical Manual of Mental Disorders (DSM- IV) defines nocturnal enuresis as an involuntary voiding of urine during sleep, with a severity of at least twice a week, in children aged >5 years in the absence of congenital or acquired defects of the central nervous system ²⁷.

Butler (2005) ²⁷ makes a distinction between nocturnal enuresis and infrequent bedwetting. Nocturnal enuresis is defined as in the DSM-IV definition i.e. wetting at least twice a week and infrequent bedwetting as less than twice a week. This distinction is considered to have value as infrequent bedwetting is common in younger children but the prevalence falls sharply between 4 and 6 years of age, whereas children with more frequent wetting are more likely to have persisting symptoms.

The International Children's Continence Society (ICCS) have worked to standardise descriptions of lower urinary tract symptoms and conditions in children ¹¹⁴. Their main aim is to promote standardisation of terms and definitions used in research studies so that it is easier to compare studies and understand the population groups included. The ICCS considers that terms should be descriptive rather than express or imply underlying causes; that where possible terminology should be similar to that used when describing adult bladder function and that correct descriptive terms should not require invasive or complicated testing. The ICCS acknowledge that terms that have been used for many years and have been accepted cannot simply be discarded. The ICCS promote the use of the term incontinence when describing uncontrollable leakage of urine. Enuresis is defined as intermittent incontinence of urine when sleeping, with 'nocturnal' added for greater clarity if needed. The ICCS suggest using the term mono-symptomatic enuresis to signify that children have problems only when asleep; the term non-mono-symptomatic enuresis describes the symptoms of children who have urinary incontinence at night and also have day time symptoms. Nocturnal can be included as in mono-symptomatic nocturnal enuresis (MNE) and non-mono symptomatic enuresis (NMNE).

One of the important aspects in the management of lower urinary tract symptoms in children is the recognition that symptoms which may be considered normal in a

younger child may be considered pathological in an older child. The DSM –IV definition of Nocturnal Enuresis uses an age of > 5 years.

2.1.4 Pathophysiology and targeting of treatment

The causes of bedwetting are not fully understood. Bedwetting is best considered as a symptom that may result from a combination of different predisposing factors ¹¹². There are a number of different disturbances of physiology that may be associated with the development of bed wetting. These disturbances may be categorised as:

1. Sleep arousal difficulties – a reduced ability to wake to noise or to bladder contractions.
2. Polyuria – the production of larger than normal volumes of urine overnight that typically exceed the nocturnal bladder capacity.
3. Bladder dysfunction – most often either a small bladder capacity or overactive bladder.

A variety of factors are associated with bedwetting. There is frequently a strong family history of bedwetting and genetic studies have reported linkage to a number of different gene loci ⁴⁶. There is an association between bedwetting, daytime urinary symptoms and daytime soiling. In the ALSPAC cohort 3.3% of children had both daytime wetting and bedwetting at 7 years and 6 months, with 2.3% having both daytime soiling and bedwetting. Daytime urgency increased with severity of bedwetting and occurred in 28.9% of children with NE (defined in the study according to DSM –IV) ²⁷.

In Attention Deficit and Hyperactivity Disorder (ADHD) there is an incidence of NE of around 10% ⁴⁸. The association of bedwetting with disorders with attentional problems links with the arousal difficulties considered important in pathophysiology of bedwetting. It is a significant feature for some children with difficult to manage NE.

Identifying the likely underlying mechanism for the wetting may allow better use of certain treatments. Unfortunately the clinical features do not often lead to a clear differentiation of underlying pathological mechanisms. The quality of much of the clinical research is poor with low numbers and inadequate description of symptoms in the study populations. To date the studies are not adequate to assess the treatment hypotheses generated from current physiological understanding.

Current understanding of pathophysiology suggests that a history of bedwetting without daytime symptoms makes polyuria more likely and these children may respond better to desmopressin than those who have bladder disturbances ¹¹².

Children with bladder difficulties, either overactive bladder or small bladder capacity respond less well to desmopressin^{50,119}. Some will have daytime symptoms (urinary urgency, frequency, wetting, urge incontinence hesitancy, poor urinary stream, abdominal straining) but others have an isolated night time disorder¹⁶³. Nocturnal polyuria may be diagnosed using overnight nappy weights and history, fluid intake / bladder diaries will identify most children with bladder dysfunction although some children will need detailed urodynamics.

The ICCS¹¹⁴ now recommends that all research studies properly define their patients by screening for daytime symptoms and measurement of overnight urine production. This is thought to be particularly important when evaluating drugs that treat polyuria (e.g desmopressin) and drugs for overactive bladder (e.g anticholinergics). Historically this has not been done although many studies have identified the presence or absence of daytime wetting (one symptom of bladder dysfunction).

2.2 Approach of this Guideline

This guideline aims to provide advice on the assessment and management of children and young people with bedwetting. The guidance is applicable to children and young people up to 19 years with the symptom of bedwetting.

It has been common practice to define enuresis as abnormal from 5 years and only to consider children for treatment when they are 7 years. While the prevalence of symptoms decreases with age the guideline scope did not specify a younger age limit in order to consider whether there were useful interventions that might be of benefit to children previously excluded from advice and services.

For the purposes of this guideline we have used the terms 'bedwetting', and 'daytime symptoms' to describe those symptoms that may be experienced by the population who present for treatment for 'bedwetting'. This terminology is used for clarity and as it is an accurate representation of the populations included in the research evidence.

While the ICCS now recommends that all children included in studies have their night and day time symptoms properly recorded, this has been a recent development. Research evidence clearly defining children as mono-symptomatic or non-mono-symptomatic is not available for most of the potential interventions. Some studies explicitly state that they excluded children with daytime wetting. We classified these as studies where the population had bedwetting or nighttime wetting only. We acknowledge that some of these children may have had daytime symptoms other than wetting such as urgency or frequency. The remainder of studies did not report either including or excluding daytime wetting or symptoms and we considered them as studies where the population had bedwetting with possible daytime symptoms.

The evidence is therefore reported as follows:

- **Monosymptomatic:** If the study explicitly reported the children had monosymptomatic nocturnal enuresis the study was classed as children having monosymptomatic nocturnal enuresis.
- **Non-mono:** There were no studies which described children as having non-monosymptomatic nocturnal enuresis.
- **Studies including bedwetting only:** If the study explicitly reported that they excluded children with daytime wetting, or reported there were no children with daytime wetting the study was classed as a study which only included children with night time only wetting.
- **Studies including bedwetting with possible day time symptoms:** If the study did not report inclusion and exclusion criteria on the basis of the timing of the wetting by the child, or if the study inclusion reported daytime wetting or the baseline characteristics the study was classed as “did not positively exclude children with daytime wetting”

The presence or absence of daytime symptoms can be helpful for understanding the underlying problem and possibly for planning treatment but the management of daytime symptoms is not within the scope of this guideline.

The evidence for these different subgroups was looked at separately. However, as no significant differences were found as to warrant differential treatment, the recommendations are based on data from all subgroups.

2.3 Remit

The following remit was received from the Department of Health:

‘To develop a clinical guideline for the management of bedwetting in children.’

2.4 What is a guideline?

NICE clinical guidelines provide recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific clinical questions. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline presents the recommendations and selected research recommendations only
- the quick reference guide presents recommendations in a suitable format for health professionals
- information for the public ('understanding NICE guidance') is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE www.NICE.org.uk.

2.5 What the guideline covers

The guideline was developed in line with the guideline scope. Prior to the commencement of the guideline the scope was subject to stakeholder consultation

in accordance with processes established by NICE in the guideline manual. The scope is included in Appendix A and summarized below.

2.5.1 Groups

- a) Children and young people aged under 19 years who continue to have episodes of night-time bedwetting, with or without daytime urinary symptoms.
- b) Children and young people aged under 19 years with special needs who continue to have night-time bedwetting with or without daytime urinary symptoms.

An upper age of 19 is used to as the guideline includes young people with and without special needs. Educational and social services commonly continue for children with special needs up to 19 years. The age range used was agreed with NICE following stakeholder comments on the scope.

2.5.2 Clinical management

The aspects of clinical management included are:

Assessment of the child or young person

Support, advice, information and follow-up for children and young people, parents and carers.

Lifestyle and behavioural interventions.

Treatments based on enuresis alarms.

Pharmacological interventions.

Other interventions, including:

- educational interventions (for example, providing information)
- counselling
- psychotherapy
- cognitive therapy

Interventions for prevention of relapse.

2.6 What the guideline does not cover

2.6.1 Groups

- a) Adults aged 19 years or over with any form of incontinence.
- b) Children and young people who have daytime urinary incontinence only.

2.7 Guideline Limitations

Guideline limitations are as follows:

- NICE clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with health services and so recommendations are not provided for social services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.
- It is not possible in the development of a clinical guideline to complete extensive systematic literature reviews of all pharmacological toxicity. NICE expects the guidelines to be read alongside the summaries of product characteristics.

2.8 Who developed this guideline?

2.8.1 The National Collaborating Centre for Primary Care/National Clinical Guidelines Centre

This guideline was commissioned by NICE from the National Collaborating Centre for Primary Care (NCC-PC). On 1st April 2009 the NCC-PC merged with 3 other collaborating centres to form the National Clinical Guidelines Centre (NCGC). The development of this guideline was therefore started at the NCC-PC and completed at the NCGC. The NCGC is one of four centres funded by NICE and comprises a partnership between a variety of academic, professional and patient-based organisations. As a multidisciplinary centre we draw upon the expertise of the healthcare professions and academics and ensure the involvement of patients in our work.

2.8.2 The development team

The development team had the responsibility for this guideline throughout its development. They were responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to

consultation comments. The development team working on this guideline consisted of the:

- **Guideline lead**
who is a senior member of the NCGC team who has overall responsibility for the guideline
 - **Information scientist**
who searched the bibliographic databases for evidence to answer the questions posed by the GDG
 - **Reviewer (Health Services Research Fellow)**
with knowledge of the field, who appraised the literature and abstracted and distilled the relevant evidence for the GDG
 - **Health economist**
who reviewed the economic evidence and assisted the GDG in considering cost-effectiveness
 - **Project manager**
who was responsible for organising and planning the development, for meetings and minutes and for liaising with the Institute and external bodies
 - **Chair**
who was responsible for chairing and facilitating the working of the GDG meetings
- The members of the development team attended the GDG meetings and participated in them. The development team also met regularly with the Chair of the GDG during the development of the guideline to review progress and plan work.

2.8.3 The Guideline Development Group (GDG)

A Chair was chosen for the group and his primary role was to facilitate and chair the GDG meetings.

The GDG consisted of a diverse multidisciplinary group with an interest and/or expertise in Nocturnal Enuresis. The Chair who oversaw the work, Dr Jonathan Evans, works as a NHS Consultant Paediatric Nephrologist at The Children and Young Peoples Kidney Unit Nottingham University Hospitals. Dr Evans chairs the British Association for Paediatric Nephrology Registry Group and is a member of the Royal College of Paediatrics and Child Health Quality of Practice Committee. Dr Evans has co-authored seven Cochrane Systematic Reviews, has developed many clinical guidelines locally and was a member of the NICE guideline development group for Anaemia Management in Chronic Kidney Disease.

The professional representatives on the Group were chosen according to a set process. The NCCPC project team decided on the necessary professional representation required for the GDG, based on the scope of the guideline. Professional registered stakeholder organisations were written to notify them of the

advertisement and recruitment process. Once all of the applications were received, the NCC-PC Chief Executive, Chairman and the Project Lead selected the individual members, on the basis of their CV's, supporting statements, and against a selection criteria adapted from the person specification and job description.

For the patient members, the PPIP at NICE submitted the received applications, from which the Chairman and the Guideline Lead chose two as patient members based on the aim (as with the professional healthcare applicants) of including as wide a range as possible of expertise, experience, and professional and geographic representation from across England and Wales.

Applicants who were not selected for the GDG were invited to act as Expert Peer Reviewers and were sent drafts of the guideline by the Institute during the consultation periods and invited to submit comments using the same process as stakeholders.

In accordance with guidance from NICE, all GDG members' and chairman declared in writing interests that covered consultancies, fee-paid work, share-holdings, fellowships, and support from the healthcare industry and these were made available in the public domain. Details of these can be seen in Appendix E. Declaration of interests were updated at the start of each GDG meeting. A record of updated declarations of interest was recorded in the NCGC's database and the minutes of each meeting were produced. The minutes of the GDG meetings were published on the NICE website within 2 weeks of being agreed by the GDG. The Chair and each GDG member received a copy of The Guidelines Manual (January 2009) once this was updated.

The names of GDG members appear listed below.

Full GDG members

Dr Jonathan Evans (Chair)

Consultant Paediatric Nephrologist Nottingham Children's Hospital, Nottingham University Hospitals NHS Trust

Dr Anne Wright

Consultant Paediatrician, Children's Bladder Clinic
Evelina Children's Hospital, Guy's and St. Thomas' Foundation NHS Trust

Mrs Charlotte Mawby

Senior Clinical Specialist Nurse Advisor in Paediatric Continence
Community Health Oxfordshire, Hosted by Oxfordshire Primary Care Trust Jubilee House

Mrs Deborah Chippington-Derrick

Parent and Carer Member
Company Director/Software Engineer
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Mrs Janet Wootton

Specialist Enuresis Nurse School Health Nurse
York Hospital NHS Foundation trust

Dr Patricia Hall

Chartered Clinical Psychologist
Sheffield Children's NHS Foundation Trust

Dr Penelope Dobson MBE

Patient Member
Founder and former director of the children's charity ERIC (Education and Resources for Improving Childhood Continence) and currently chair of the Paediatric Continence Forum (PCF)

Mrs Philippa Williams

Parent and Carer member
Project Worker, The Fostering Network

Dr Mark Mac Kenzie

General Practitioner
Albany House Medical Centre,

Mrs Sally Norfolk

Operational Lead School Nursing, Children and Family Services. NHS Leeds
Community Healthcare

Dr Ursula Butler

Consultant Community Paediatrician
Clinical Lead Community Continence Service, Sheffield Children's NHS Foundation Trust

Co-opted Experts

Mrs Anne Longton

Clinical Lead Health Visiting (East Sussex Downs and Weald PCT)

NCGC-ACC staff

Dr Norma O'Flynn

Guideline Lead and Clinical Director

Ms Vanessa Nunes

Senior Health Services Research Fellow/Project Manager

Ms Katrina Sparrow

Health Services Research Fellow

Ms Laura Sawyer

Health Economist

2.8.4 Guideline Development Group meetings

The GDG met on eleven occasions at approximately 6 weekly intervals over a period of fifteen months to review the evidence identified by the project team, to comment on its quality and completeness and to develop recommendations for clinical practice based on the available evidence. The final recommendations were agreed by the full GDG.

2.9 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

2.9.1 What elements of multi-component treatments (for example dry bed training and retention control training) are clinically effective and cost effective for treating bedwetting in children and young people under 19 years old?

Why this is important

The elements of multi-component treatments (for example dry bed training and retention control training) that are clinically effective and cost effective for treating bedwetting in children and young people under 19 years old is not known. Data from randomised controlled trials of dry bed training and retention control training suggest that the treatments may be clinically effective. However certain elements of the multi-component treatments are not acceptable as a form of treatment due to their punitive nature, it is not known which elements of the treatments are effective and therefore could be used in the treatment of nocturnal enuresis.

Research should:

- Use randomised controlled trials to test the effect of the different elements of dry bed training alone and in different combinations for the treatment of bedwetting.
- Use randomised controlled trials to test the effect of the different elements of retention control training alone and in different combinations for the treatment of bedwetting
- Consider different age groups of children being treated, such as young children aged less than 7 years and older children aged over 10 years as the ability of children to take responsibility for behaviours may be important.

- Clearly describe the techniques including who gave instructions, the timing of the treatments and the setting.

Outcomes of interest include: the number of children who achieved 14 consecutive dry nights, the number of children who remain dry at 6 months and 2 years after treatment, the mean number of wet nights after treatment, the change in the number of wet nights, the psychological effect of treatment, psychological effects (self-esteem, self-concept, PinQ), quality of life measure and drop outs.

2.9.2 What is the clinical and cost effectiveness of standard interventions e.g. alarm and desmopressin for treating bedwetting in children and young people under 19 years old?

Why this is important

The evidence base for management of bedwetting is poor. Studies are inadequately powered, symptoms are poorly defined and study populations are commonly children seen in secondary and tertiary centres. Follow up periods are often inadequate.

Research should:

- More subgroup data (young children, children with daytime symptoms as well as bedwetting, children who were previously successful with subsequent relapse, children with sickle cell disease, severe wetting, special needs,
- More robust statistical data in trials of standard interventions for treating bedwetting (e.g. adequately powered to detect differences)
- Data on longer term follow up
- Data from populations on a primary care/community care level

2.9.3 What is the clinical and cost effectiveness of desmopressin versus combination desmopressin plus night-time only tolterodine/oxybutynin in children with non-monosymptomatic nocturnal enuresis?

Why this is important?

Children with non-monosymptomatic nocturnal enuresis (NME) are estimated to make up one third of the population of children with enuresis and are considered more resistant to treatment than monosymptomatic enuresis. The combination of an anticholinergic agent and desmopressin at night-time for this group should theoretically work to stabilise the bladder and increase bladder capacity in addition to decreasing nocturnal urinary production. One previous trial found that the combination of oxybutynin and desmopressin in a group of children with NME was significantly more effective versus desmopressin after one month of treatment but not at six months of treatment. Further studies are needed to corroborate this study both using night-time only oxybutynin or longer-acting night-time only tolterodine combined with desmopressin versus desmopressin alone in the NME group of children.

Research should:

Use a double-blind randomised control trial of medication (as above) in children with NME

Research outcomes should include:

- Number of children achieving 14 consecutive dry nights
- Average reduction in wet nights at the end of treatment
- Increase or change in maximum voided volume as estimated by Bladder diary before and after treatment
- Side effects of the medication
- Relapse after six months of treatment
- Quality of life measures and costs

2.9.4 What is the impact of bedwetting upon the psychological functioning and quality of life of children and their families? How do these change with treatment?

Why is this important?

There are relatively few studies which focus upon the psychological impact and health-related quality of life of children who experience bedwetting. In addition, studies of effectiveness have focused on the achievement of dryness as the primary outcome rather than how treatment might affect social and psychological aspects as well as the quality of life of children and their families.

Research should:

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- Examine the psychological impact and quality of life of children and their families as well as the effectiveness of treatment upon these aspects.
- Use standardised measures to assess the psychological impact of bedwetting on children as well as the QoL of the child and family.
- Use standardised measures to assess change associated with treatment for bedwetting.

Quality of life research of children with bedwetting pre- and post- treatment would also be very useful in informing further economic evaluation work in the area.

2.9.5 What is the effectiveness of psychological therapies in the treatment of bed-wetting? Which psychological therapy is most useful? For which clinical groups would psychological therapies be the most appropriate intervention?

Why is this important?

There is some evidence that CBT may be useful as a treatment in children with severe bed-wetting, however, there are few robust studies that examine the effectiveness of CBT for other clinical groups or psychological therapies more widely as treatment for bed-wetting.

Research should:

- Use rigorous methodology, ideally with comparison of control and other interventions.
- Provide clear descriptions of specific psychological interventions with reference to theoretical frameworks.
- Specify particular clinical groups of interest within the bed-wetting population with respect to aspects such as previous treatment and development.
- Outcomes may also examine aspects other than night time dryness such as quality of life for the child and family.
- Examine long-term outcome.

2.9.6 What is the effectiveness of complementary therapies (acupuncture and hypnotherapy) for reducing the number of wet beds and improving self esteem in children who wet the bed when they are use independently or in conjunction with conventional treatments?

Why this is important

Many families consider the use of complementary and or alternative medicine (CAM) as a treatment options when conventional treatment 'fails' or in order to avoid drug or other treatments. There is very little evidence about the efficacy of many complementary and alternative treatments but the use of CAM is widespread and increasing across the developed world. There is a clear need for more effective guidance for the public and health professionals who advise patients as to what does and does not work and what is and is not safe.

Research should:

- Use RCTs to test the effect of using complementary and/or alternative therapies in addition to or instead of other treatments for bed-wetting.
- Clearly describe the complementary or alternative therapies tested, including the provision of the treatment for both the treatment and the control group.
- Priority should be given to acupuncture and hypnotherapy in further research but should not exclude other complementary or alternative therapies.
- If possible the comparative effectiveness and cost effectiveness of different complementary or alternative therapies should be tested.
- Outcomes of interest include: self esteem, increase in no. of dry nights, permanent or temporary nature of increased no. of dry nights, quality of life, costs and social engagement.

2.9.7 What is the prevalence of wetting/soiling in adolescence and what are the long term consequences for adolescents with these problems?

Why this is important

There is evidence that, for an important minority of children, wetting and soiling problems persist into late childhood and sometimes beyond puberty, but their prevalence is not clearly known. It has also recently been reported that children who experience more frequent bedwetting (more than three times a week) are more likely to persist with the problem into late childhood and adolescence. These studies suggest that, contrary to popular belief, wetting and soiling problems do not always resolve with increasing age. If wetting/soiling problems remain unresolved or untreated they can become socially and psychologically debilitating. There are no longitudinal cohort studies examining the impact of wetting and soiling on a wide range of outcomes in adolescence relating to mental health, education/school attainment, relationships with parents and peers, social activities and goals/aspirations for the future. Persistence of wetting/soiling problems into this phase is likely to be accompanied by ridicule and bullying by peers and increasing intolerance from parents, especially if they believe that their child is to blame for

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their problem. Such reactions can only serve to exacerbate the child's distress and may lead to delays in seeking help. In particular, teenagers who are unsuccessfully treated in childhood are often reluctant to seek help for wetting or soiling due to the severe embarrassment associated with the problem, and others may simply believe that no help is available.

Research should:

- Use adolescents own self-reports of frequency of bedwetting, daytime wetting and soiling in this age group
- Adapt existing trajectory models to incorporate information on frequency of wetting and soiling to examine whether children with more frequent problems are more likely to experience continuing wetting and soiling into adolescence.

Outcomes of interest include: the examination of mental health, psychosocial and educational outcomes and whether adolescents who have combined wetting and soiling are at increased risk of negative outcomes compared to those with wetting or soiling alone.

2.10 Acknowledgements

We gratefully acknowledge the contributions of the following people:

Ms Julie Neilson, Dr Grammati Sari, Ms Sarah Willett, Mr Andrew Gyton, Ms Sarah Willis, Dr Alec Miners, Dr David Wonderling, Dr Ipek Akil.

2.11 Glossary

Absolute risk reduction (Risk difference)	The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Adherence	The extent to which the patient's behaviour matches the prescriber's recommendations. Adherence emphasises the need for agreement and that the patient is free to decide

whether or not to adhere to the doctor's recommendation.

Adjustment	A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.
Alarm	See enuresis alarm.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Audit	See 'Clinical audit'.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Bladder diary	A diary that records voiding times and voided volumes, leakage episodes, pad usage and other information such as fluid intake, degree of urgency, and degree of incontinence. See also

frequency-volume chart.

Bladder training	Bladder training (also described as bladder retraining, bladder drill, bladder re-education, bladder discipline) actively involves the individual in attempting to increase the interval between the desire to void and actual void.
Bedwetting	Term used in this guideline to describe discrete urinary incontinence occurring during sleep; synonymous with enuresis and with nocturnal urinary incontinence
Blinding (masking)	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Capital costs	Costs of purchasing major capital assets (usually land, buildings or equipment). Capital costs represent investments at one point in time.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Charts	See frequency- volume charts
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.

Clinical impact	The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes, of the target population.
Clinical question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Cluster	A closely grouped series of events or cases of a disease or other related health phenomena with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation.
Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Co-morbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or

outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.

Consensus methods	Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial (CCT)	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of

effectiveness.

Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible interval	The Bayesian equivalent of a confidence interval.
Daytime frequency	The number of voids recorded during waking hours and includes the last void before sleep and the first void after waking and rising in the morning.
Daytime Symptoms	Refers to the presence of lower urinary symptoms which include urinary urgency, frequency, poor urinary stream, the need for abdominal straining to void and urinary incontinence
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Decision problem	A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.

Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Double blind/masked study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment nor intervention the subject is receiving. The purpose of blinding/masking is to protect against bias.
Drop-out	A participant who withdraws from a clinical trial before the end.
Dry bed training	A training programme that combines a number of different behavioural interventions that may include rewards, punishment training routines and waking routines and be undertaken with or without an enuresis alarm
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effect size	<p>This term is usually used in meta-analysis to denote treatment effect, or estimate of effect.</p> <p>It also refers to standardised mean difference (SMD), obtained by dividing the mean difference with the pooled standard deviation. This is the meaning usually referred to in GRADE.</p>
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.

Enuresis	Intermittent incontinence in discrete episodes when asleep; see bedwetting; see nocturnal enuresis
Enuresis alarm	A battery powered alarm that is triggered by urine coming into contact with the alarm sensor. Alarms come in 2 main groups: bed alarms where the sensor pad is placed under a draw sheet and body worn alarms where the sensor is placed eg between two pairs of snugly fitting underpants. The alarms can generate various noises or sometimes pre recorded sounds. Some body worn alarms can be set to vibration with or without sound
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
Equity	Fair distribution of resources or benefits.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Expert consensus	See 'Consensus methods'.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.

Follow up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Frequency-volume charts	Preferred term of the International Children’s Continence Society (ICCS) for charts to be completed by child and parents/carers to record urinary symptoms during treatment.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard	See ‘Reference standard’.
Goodness-of-fit	How well a statistical model or distribution compares with the observed data.
Grading of Recommendations Assessment, Development and Evaluation (GRADE)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems.
Guideline Development Group	The GDG agrees the review questions, considers the evidence and develops the recommendations. Membership of the GDG therefore needs to be multidisciplinary, comprising: <ul style="list-style-type: none">• healthcare professionals (both specialists in the topic and generalists)• patients and/or carers• the technical team (systematic reviewer, information

specialist, health economist).

Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Homogeneity	This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Imprecision	Imprecision is one of the quality elements considered under the GRADE system. Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.

Incremental cost effectiveness ratio (ICER)	<p>The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.</p> $\text{ICER} = (\text{Cost}_A - \text{Cost}_B) / (\text{Effectiveness}_A - \text{Effectiveness}_B).$
Inconsistency	<p>Inconsistency is one of the elements of quality considered under the GRADE system. Inconsistency refers to the unexplained heterogeneity in the results observed.</p>
Indirectness	<p>Indirectness is one of the elements of quality considered under the GRADE system. Indirectness of evidence refers to the difference in study population, intervention, comparator and outcomes between the available evidenced and the clinical question or population addressed in the guideline recommendations.</p>
Indication (specific)	<p>The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).</p>
Intention-to-treat analysis (ITT analysis)	<p>An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.</p>
Intermediate outcomes	<p>Outcomes that are related to the outcome of interest but may be more easily assessed within the context of a clinical study. The reduction of prostate volume which in turn is related to the reduced risk of acute urinary retention.</p>
Internal validity	<p>The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study's findings. See 'External validity'.</p>
Intervention	<p>Healthcare action intended to benefit the patient, for example,</p>

	drug treatment, surgical procedure, psychological therapy.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Lifting	Lifting is carrying or walking a child to toilet. Lifting without waking means that effort is not made to ensure the child is fully woken.
Likelihood ratio (LR)	The ratio of the probability that a person with a condition has a specified test result to the probability that a person without the condition has the same specified test result. For positive test results, this is referred to as "Likelihood ratio positive", LR+. For negative test result, this is known as "Likelihood ration negative", LR-.
Literature review	An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.
Markov model	A method for estimating long term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Medical devices	All products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or handicap.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Minimal important difference (MID)	This is the smallest change which can be recognised by a patient as being clinically significant

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Monosymptomatic Nocturnal Enuresis	Nocturnal Enuresis without any daytime urinary symptoms (see daytime symptoms).
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Narrative summary	Summary of findings given as a written description.
Network Meta-analysis (NMA)	Type of analysis that allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different interventions in order of efficacy.
National Clinical Guideline Centre (NCGC)	Centre commissioned by NICE to develop the nocturnal enuresis guideline.
Nocturnal enuresis	Enuresis is intermittent incontinence in discrete episodes when asleep; the term nocturnal is often used for clarity
Non-monosymptomatic Nocturnal Enuresis	Nocturnal Enuresis with associated daytime urinary symptoms
Nocturnal polyuria	Nocturnal urine output exceeding 130% of expected bladder capacity
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case-control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.

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Off-label	A drug or device used treat a condition or disease for which it is not specifically licensed.
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the loss of other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Overactive Bladder	Bladder condition where main symptom is urgency and symptoms may include have frequency and wetting
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
Partial Response	Partial response is 50% reduction in wet nights; or a response less than 14 dry nights or 90% improvement in symptoms.
Pin Q	A continence-specific paediatric quality-of-life measurement tool.
P value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Polysymptomatic	See non-mono symptomatic nocturnal enuresis
Polyuria	See nocturnal polyuria
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Placebo effect	A beneficial (or adverse) effect produced by a <i>placebo</i> and not due to any property of the <i>placebo</i> itself.
Primary care	Describes services that patients have access to without requiring referral from another health care professional.

	Primary care is usually delivered outside hospitals and primary care includes GPs, , dentists, pharmacists and opticians.
Primary research	Study generating original data rather than analysing data from existing studies (which is called secondary research).
Product licence	An authorisation from the MHRA to market a medicinal product. A drug may be “licensed” for several conditions. When a drug is referred to as “unlicensed” for a particular indication, that means that the may have a marketing authorisation for other conditions, but not for the condition discussed. This is also known as “off label” use.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are <i>retrospective</i> .
Quality of life	See ‘Health-related quality of life’.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient’s quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up

	to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Remit	The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address.
Recurrence of bedwetting	Describes children who have responded to children but bedwetting recurs when active treatment stops
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Response to treatment	Response to treatment was measure by attainment of 14 dry nights or 90% reduction in wet nights.
Retention control training	Training routines to improve the ability to defer the need to pass urine
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are <i>prospective</i> .
Review of the literature	An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.
Secondary bedwetting	Bedwetting that has occurred after a child has been dry at night for more than 6 months
Secondary benefits	Benefits resulting from a treatment in addition to the primary, intended outcome.
Selection bias (also allocation bias)	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with

	concealed allocation) of patients protects against this bias.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity	<p>Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects.</p> <p>See the related term 'Specificity'</p>
Sensitivity analysis (SA)	<p>A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.</p> <p>One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.</p> <p>Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.</p> <p>Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.</p> <p>Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).</p>
Severe Wetting	Bedwetting that occurs more than five times a week.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.

Statistical power	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Synthesis of evidence	A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Time horizon	The time span used in the NICE appraisal which reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Urgency	The sudden and unexpected experience of an immediate need to void
Urinalysis	A test undertaken by dipping a chemical reagent stick into a sample of urine in order to detect substances that may indicate a disease (i.e protein blood or glucose) or urine infection (i.e leucocyte esterase, nitrites)
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Vesico-urethral	Relating to, or connecting the urinary bladder and the urethra.
Voiding	Passing urine – “weeing” The phase during which the bladder expels its contents (urine).

Waking

Waking means waking a child from sleep to take them to the toilet.

3 Methods

3.1 *Guideline methodology*

The Nocturnal Enuresis guideline was commissioned by NICE and developed in accordance with the guideline development process set out by 'The guidelines manual'¹¹⁰. The versions of the guideline manual used for each stage of guideline development are detailed in table.

Table 3-1: Version of NICE guideline used

Stage of development	Version of NICE Guidelines Manual Used
Scope	April 2007
Formation of GDG	April 2007
Review of evidence and drafting of recommendations	April 2009 Pilot for GRADE
Consultation	January 2009

3.2 *Process of guideline development*

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guidelines Centre (NCGC).
- The NCGC establishes a guideline development group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

3.3 *Developing the clinical questions*

A series of questions created from the scope was the first step in the development of the guideline. The questions formed the starting point for the evidence reviews and facilitated the development of recommendations by the GDG.

The questions were developed by the project team with the guidance from the GDG. Where possible, the questions were refined into specific research questions by the project teams to aid literature searching, appraisal and synthesis. The full list of questions is shown in appendix B.

Reviews of the evidence using systematic methods of searching and appraisal were conducted to answer the clinical questions in line with the guidelines manual. The GDG and development teams agreed appropriate inclusion and exclusion criteria for each topic area in accordance with the scope.

3.4 Outcomes

Review questions are formulated according to PICO (patient, intervention, comparators, outcome) framework. The outcomes preferred by the GDG are listed below.

3.4.1 Assessment outcomes

The outcomes that we looked for in the questions related to assessment were:

- Excluding secondary causes
- Establish pattern of wetting to include:
- Overactive bladder
- Constipation

3.4.2 Clinical effectiveness of interventions

When considering interventions the GDG was primarily interested in the achievement of sustained dryness as this was likely to be the initial expectation from treatment of children and their families. The GDG considered that a combination of outcomes would provide a full assessment of the clinical effectiveness of interventions for nocturnal enuresis. Children and families may be interested in early short term improvements for practical reasons. However for children with severe nocturnal enuresis a percentage improvement may also be valuable.

The GDG considered that 14 consecutive dry nights indicated successful treatment. International Childhood's Continence Society (ICCS) guidelines suggest >90% improvement is a success and 50-90% is a partial success. Longer term outcomes included were relapse at 6 and 12 months. The GDG also included the psychological effects and impact on quality of life treatments have on children with nocturnal enuresis as important outcomes. The outcomes of drop out rates and adverse events

were chosen to show any negative effect a treatment may have. Specific adverse events were chosen according to the treatment being reviewed with known adverse events or suspected adverse events being evaluated.

The primary outcomes in all questions related to clinical effectiveness of interventions were

- Dry for 14 consecutive nights
- Dry for 6 consecutive months (continuing success)

We looked for the following secondary outcomes:

- >90% improvement
- 50-90% improvement
- Relapse at 6 months or after 12 months
- Reduction/change in number of wet nights (reported in earlier studies) This outcome is represented in the GRADE tables as reduction in number of wet nights as a mean difference between the two comparisons. The additional figures in GRADE represent the number of participants for which the assessment of outcome was available at the end of receiving treatment.
- Dry for 2 consecutive years
- Adverse events
- Psychological effects (self-esteem, self-concept, PinQ)
- Quality of life measure
- Drop-outs
- Behaviour changes
- Continued success
- Relapse prevention

3.5 Choice of subgroups

The GDG were interested in providing appropriate recommendations for children and young people who might have specific needs e.g. in relation to co-morbidities. The following subgroups were included as subgroups when the evidence was reviewed:

Table 3-2: Guideline Subgroups

Subgroup	Rationale
Children with daytime symptoms as well as bedwetting	Current understanding of pathophysiology suggests this group may respond differently to treatment.
Young children (under 7 years).	Traditionally children have not been considered for treatment of bedwetting until they are 7 years. The GDG considered that this may not be appropriate and left parents/carers and children without advice and treatment. This subgroup was where papers specifically looked for young children or where the mean age was under 7 years. If the mean age was over 7 years the results were included in the general population group or other specific sub groups.
Special needs (learning disabilities, emotional and ADHD)	Bedwetting is common in this population
Severe wetting (6-7 nights a week)	The GDG were interested in whether this group required different management approach
Previously successful and with subsequent relapse	Relapse is common and GDG wished to evaluate choice of subsequent treatment
Children with sickle cell disease.	The GDG considered that healthcare professionals have been cautious about the use of drugs in the treatment of bedwetting in children with enuresis because of concern about the impact of fluid restriction on children with sickle cell disease.

3.6 Literature search strategy

3.6.1 Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder (now NHS Evidence), National Guidelines Clearinghouse, Scottish Intercollegiate Guidelines Network (SIGN), Guidelines International Network (GIN), Canadian Medical Association (CMA) Infobase (Canadian guidelines), National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines (Australian Guidelines), New Zealand Guidelines Group, BMJ Clinical Evidence, TRIP database, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), DH Data, Medline and Embase.

3.6.2 Evidence review for guideline development

The aim of the evidence review was to identify the most relevant, published evidence in relation to the key clinical questions generated by the GDG. Reviews of the evidence using systematic methods relating to searching and appraisal of the evidence were conducted.

The following bibliographic databases were searched from their inception to the latest date available: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Database (HTA), CENTRAL (Cochrane Controlled Trials Register). MEDLINE, EMBASE, CINAHL and PsycINFO

The scoping searches had retrieved a number of Cochrane reviews therefore an update search was carried out in October 2008 to locate new systematic reviews or randomised controlled trials of interventions. The Cochrane Incontinence group search strategy was adapted and methodological search filters designed to limit searches to these study designs were used. These were devised by the Centre for Reviews and Dissemination and the Cochrane Collaboration. An additional search was carried out in February 2009 to find papers using other study designs.

The economic literature was identified by conducting searches in NHS Economic Evaluations Database (NHSEED), HTA database and in MEDLINE and EMBASE using an economics search strategy developed by SchARR at the University of Sheffield. Foreign language papers were excluded from all search results. All of the searches were rerun in December 2009 prior to consultation.

Databases of the results of the searches for each question or topic area were created using the bibliographic management software Reference Manager.

The search strategies for all questions or topic areas developed for the Medline database are detailed in appendix B. Details of all literature searches for the evidence reviews are available from the NCGC. Further references were also suggested by the GDG.

3.7 Assessing quality of evidence

Two stages of quality assessment were conducted. At the first stage, studies were quality assessed and only included in the review and meta-analysis if they met quality criteria. Data from these studies were then extracted and the outcomes of interest were pooled. At the second stage, the quality of evidence for each of these outcomes was then quality assessed using elements of the GRADE system. Please refer to section 3.8 of the guideline for further details or to section 6.7 in the NICE Guidelines Manual (2009) for relevant publications related to GRADE.

3.7.1 Quality assessment for inclusion of studies

All studies were quality assessed before being included as part of the systematic review. The criteria for assessment for different types of studies are listed below.

For each clinical question the highest level of evidence was sought. We searched for observational data where RCT data was not available and the question was of significant importance in forming recommendations (e.g. any missing subgroups listed in the clinical questions). The quality assessment criteria as listed in the NICE Guidelines Manual 2009 were used to assess randomised controlled trials and observational studies. Please refer to Guidelines Manual (2009) for further detail.

3.7.2 General overview of the quality of the evidence for NE

The GDG considered that the vast majority of the retrieved RCTs were not sufficiently powered to show a statistically significant difference between the interventions. Given the small number of participants in many studies the conclusions derived from such studies required caution. The observational studies that were retrieved were also of low methodological quality with small numbers of participants and inadequate description of participants' symptoms.

Many studies did not report the statistics that allow calculation or estimation of the standard deviations (e.g. confidence intervals, standard errors, t values, p values, F values). Section 3.9.2 outlines the process followed in these situations.

Despite the low quality of studies retrieved the GDG considered it important to include them as they are currently the best evidence available and most current

clinical practice is based on these studies. The GDG considered that critically appraising this evidence was necessary to inform health professionals working in this area.

3.8 GRADE (Grading of Recommendations, Assessment, Development and Evaluation)

The evidence for outcomes from RCTs which passed the quality assessment were evaluated and presented using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (<http://www.gradeworkinggroup.org/>). The software (GRADEpro) developed by the GRADE working group was used to assess pooled outcome data using individual study quality assessments and results from meta-analysis.

The summary of findings was presented as two separate tables in this guideline. The "Clinical Study Characteristics" table includes details of the quality assessment, which can be found in appendix H, while the "Clinical Summary of Findings" table includes pooled outcome data, an absolute measure of intervention effect calculated and the summary of quality of evidence for that outcome. This table is included in the full guideline evidence reviews. In this table, the columns for intervention and control indicate pooled sample size for continuous outcomes. For binary outcomes such as relapse or adverse events, the event rates (n/N) are shown with percentages. Reporting or publication bias was considered in the quality assessment but not included in the Clinical Study Characteristics table because this was a rare reason for downgrading an outcome in this guideline

Each outcome was examined separately for the quality elements listed and defined for GRADE. For further details please refer to 6.7 in the NICE Guidelines Manual (2009) for relevant publications related to GRADE.

3.8.1.1 Study limitations

The main limitations considered for downgrading are listed in the following table.

Table 3-3: Main study limitations of randomised controlled trials in NE

Limitation	Explanation
Allocation concealment	Many of the studies did not report allocation concealment. This means that those enrolling patients are aware of the group to which the next enrolled patient will be allocated.

Limitation	Explanation
Lack of blinding	Many of the studies did not report blinding. This means that patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated.

Baker (1969)⁷ (waking and star chart compared to no treatment – lifting and waking review) was downgraded for limitations due to the study having an unclear description of allocation concealment and blinding

3.8.1.2 *Inconsistency*

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p < 0.05$ or I square $> 50\%$), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. On top of the I-square and Chi square values the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

3.8.1.3 *Indirectness*

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

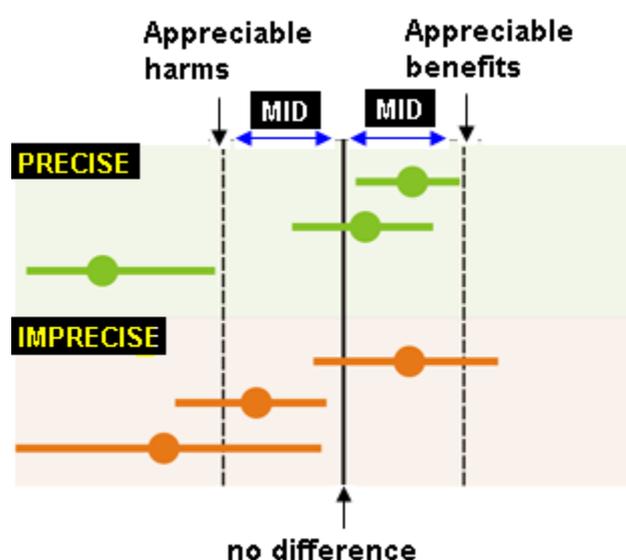
Ivester (1991)⁷⁴ (waking compared to imipramine – lifting and waking review) was downgraded for indirectness due to the treatment group being given both bladder training and random waking.

3.8.1.4 *Imprecision*

Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the minimal important difference. 95% confidence interval crosses the minimal important difference (MID), either for benefit or harm. As the MID was not known for the outcomes for NE and the use of different outcomes measures required

calculation of a standardised mean difference (SMD), the outcome will be considered for downgrading if the upper or lower confidence limit crosses a SMD of 0.5 in either direction. For dichotomous outcomes, GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk of less than 0.75 (for risk reduction) or relative risk greater than 1.25 (for risk increase). The criteria applied for imprecision were based on the confidence intervals for pooled outcomes as illustrated below:

Figure 1 : Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot.



MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results. Figure adapted from GRADEPro software.

Lee (2005)⁹⁰ (tablet desmopressin compared to imipramine – desmopressin review) was downgraded due the confidence interval crossing the MID relative risk less than 0.75 for risk reduction and relative risk greater than 1.25.

Schulman (2001)¹³⁶ and Skoog (1997)¹³⁹ (low dose tablet desmopressin compared to high dose tablet desmopressin – desmopressin review) were downgraded due the confidence interval crossing the of the standardized mean difference (SMD) and downgrade if the upper or lower CI crosses a SMD of 0.5 in either direction.

3.8.2 NICE Economic Profile

Since GRADE was not originally designed for economic evidence, the NICE economic profile was developed to present cost and cost-effectiveness estimates from published studies or analyses conducted for the guideline. As for the clinical evidence, the economic evidence has separate tables for the quality assessment and for the summary of results. Both because no published economic evidence was identified for inclusion and the comparators in the original analysis conducted for the guideline were treatment sequences, the NICE economic profile was not used to present economic evidence. Instead, quality assessment and results are summarised in a brief narrative after relevant clinical evidence. The quality assessment is based on two criteria – limitations and applicability (table 3) and each criterion is graded using the levels in table 4 and table 5.

Table 3-4: Description of quality elements for economic evidence in NICE economic profile

Quality element	Description
Limitations	This criterion relates to the methodological quality of cost, cost-effectiveness or net benefit estimates.
Applicability	This criterion relates to the relevance of the study to the specific guideline question and NICE Reference Case.

Table 3-5: Levels for limitations for economic evidence in NICE economic profile

Level	Description
Minor limitations	The study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost-effectiveness.
Serious limitations	The study fails to meet one or more quality criteria, and this could change the conclusion about cost-effectiveness
Very serious limitations	The study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost-effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.

Table 3-6: Levels for applicability for economic evidence in NICE economic profile

Level	Description
Directly	The applicability criteria are met, or one or more criteria are not met but this is

applicable	not likely to change the cost-effectiveness conclusions.
Partially applicable	One or more of the applicability criteria are not met, and this might possibly change the cost-effectiveness conclusions.
Not applicable	One or more of the applicability criteria are not met, and this is likely to change the cost-effectiveness conclusions.

An overall score of the evidence is not given as it is not clear how the quality elements could be summarised into a single quality rating.

The narrative summary of results is presented for each study and includes a brief description of incremental cost, incremental effectiveness, the incremental cost-effectiveness ratio and a discussion of uncertainty.

3.9 Evidence reviewing process

3.9.1 Clinical literature reviewing process

References identified by the systematic literature search were screened for appropriateness by title and abstract by the systematic reviewer. Studies were selected that reported one or more of the outcomes listed in section 4.4.2. Selected studies were ordered and assessed in full by the NCGC team using agreed inclusion/exclusion criteria specific to the guideline topic, and using NICE methodology quality assessment checklists appropriate to the study design. Further references suggested by the guideline development group were assessed in the same way.

3.9.2 Methods for combining direct evidence

Meta-analyses were conducted to combine the results of studies for each clinical question using Cochrane Review Manager (RevMan5) software. Relative risk (RR) was used where outcomes were dichotomous and weighted mean differences (WMD) where outcomes were continuous. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes, and the continuous outcome was analysed using an inverse variance method for pooling weighted mean differences. Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p < 0.05$ or an I-squared inconsistency statistic of $\geq 50\%$ to indicate significant heterogeneity.

Where significant heterogeneity was present, then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The standard deviations of continuous outcomes were required for imputation for meta-analysis. However, information on variability was not reported in many studies. In such cases, calculation based on methods outlined in section 7.7.3 of the Cochrane Handbook (February 2008) 'Data extraction for continuous outcomes' were applied to estimate the standard deviations if p, t or f values of the difference between two means, 95% confidence intervals or standard error of the mean (SEM) were reported. If these statistical measures were not available, then this is indicated in the evidence statements. Imputation techniques involve making assumptions about unknown statistics, and the Cochrane Handbook, advises that it is best to avoid using whenever possible.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

3.9.3 Methods for combining direct and indirect evidence

The results of conventional meta-analyses of direct evidence alone make it difficult to determine which intervention is most effective in the treatment of bedwetting. Two reasons for this include:

- Some pairs of alternative strategies have not been directly compared in a randomised controlled trial (for example, Dry Bed Training with alarm vs Desmopressin).
- There are multiple overlapping comparisons (for example, alarm vs desmopressin, alarm vs imipramine and desmopressin vs imipramine), that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different interventions in order of efficacy, defined as the achievement of a full response without the recurrence of bedwetting after treatment discontinuation. The analysis also provided estimates of effect (with 95% credible intervals⁵) for each intervention compared to one another and compared to a single baseline risk. The NMA was conducted following the review of direct evidence and the results were interpreted within the context of the direct evidence. The GDG broadly considered whether estimates of effect from the

⁵ Credible intervals are the Bayesian equivalent of confidence intervals and are based on the percentiles of the posterior distribution of the parameter of interest.

NMA trended in the same direction as estimates from the direct evidence or whether there was contradiction between results. The GDG accounted for uncertainty in the results by looking at the confidence intervals and credible intervals from the conventional meta-analysis and network meta-analysis, respectively.

The treatment effect estimates from the NMA provide a useful clinical summary of the results and were used in conjunction with the estimates from the direct evidence to form recommendations based on all the best available evidence. Furthermore, these estimates were used as measure of treatment effectiveness of first line interventions in the de novo cost-effectiveness modelling presented in appendix G.

An overview of the rationale and methods for the NMA along with a summary of results is summarised in chapter 24. A full report on the methods, assumptions, results and limitations is included in Appendix F. Readers are directed to these relevant sections following the review of direct evidence in each chapter where all or a subset of interventions met the inclusion criteria for the NMA.

3.9.4 Evidence review protocols

The following protocols were used in the development of the evidence reviews contained in this guideline:

1) Types of participants

The participants in all evidence reviews were children and young people aged under 19 years old with nocturnal enuresis (bedwetting), with the exception of the evidence review on which are the preventative, prediction or treatment options which should be considered for children under 5 years of age with nocturnal enuresis (bedwetting). For this evidence review, the participants were composed of children aged under 5 years old with nocturnal enuresis (bedwetting).

2) Types of subgroups

The following subgroups were included in each evidence review and results were reported separately in the evidence review when available:

- Day time wetting, urinary urgency and frequency
- No day time symptoms (Night time wetting only)
- Nocturnal Polyuria- large amounts of dilute urine in the first 1/3 of the night.
- Young (under 7 years)

- Children with sickle cell disease
- Special needs (learning disabilities, emotional and behavioural e.g. ADHD)
- Secondary onset
- Severe wetting (6 to 7 nights a week)
- Family history
- Previously successful with alarm and with subsequent relapse

3) Duration of studies

There was no specified time duration for the studies to be included in the evidence reviews. This applied to all evidence reviews in this guideline.

4) Types of studies

The following evidence reviews include data from RCTs only: fluid and diet, lifting, bladder training, star charts, dry bed training, alarms, desmopressin, and anticholinergics.

The following evidence reviews included data from both RCTs and observational studies: patient choice, assessment, dose escalation, treatment resistant, psychological interventions, educational interventions and information, alternative treatments, treatment resistant children and under five year olds.

5) Types of interventions

The interventions examined for each question are listed in the relevant chapters.

6) Types of outcome measures

Excluding the evidence review of assessment, the outcome measures assessed were similar for all other evidence reviews and included: the number of children who achieved 14 consecutive dry nights, 50 to 90% improvement in number of dry nights, dry for 6 consecutive months, dry for 2 consecutive years, relapse at 6 months, relapse at 12 months or over, mean number of wet nights at end of treatment, number of drop outs, adverse events, quality of life and psychological outcomes. For the evidence review on the assessment of nocturnal enuresis (bedwetting), the outcome measures were different from those employed by the other reviews in this paper and were: excluding secondary causes, the established pattern of wetting to include overactive bladder and constipation and the impact on treatment.

The following evidence reviews had additional outcome measures: the evidence review on patient choice further included patient's preference and/or choice and the evidence review on children under five years also incorporated the prevalence of nocturnal enuresis (bedwetting) in children under 5 years, the preventative effect on children developing nocturnal enuresis and the treatment effects.

3.9.5 Structure of evidence reviews

In addition to the GRADE tables used to present the data, the GDG requested a brief narrative to describe some of the main features of the retrieved evidence. The summary of findings was presented as two separate tables in this guideline. The "Clinical Study Characteristics" table includes details of the quality assessment, which can be found in appendix H, while the "Clinical Summary of Findings" table is included in the full guideline evidence reviews. The GDG also requested that where observational studies we included in the evidence reviews, a narrative summary of the findings was to be used. This was to assist their assessment of the evidence and decision-making process.

3.10 Health Economics methods

Economic evaluation provides a formal comparison of benefits and harms as well as the costs of alternative health programmes. It helps to identify, measure, value and compare costs and consequences of alternative treatment options. These outcomes are usually synthesised in cost-effectiveness (CEA) or cost-utility analysis (CUA), which reflect the principle of opportunity costs. For example, if a particular treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to re-deploy resources to other activities that yield greater health gain.

To assess the cost-effectiveness of interventions used in the treatment of bedwetting, we conducted a systematic review of the economic literature and undertook an original economic analysis.

In accordance with the NICE social value judgement the primary criteria applied for an intervention to be considered cost effective were either:

- a) The intervention dominated other relevant strategies (that is it is both less costly in terms of resource use and more clinically effective compared with the other relevant alternative strategies); or
- b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy (or usual care).

3.10.1 Health Economic evidence review methodology

The following information sources were searched:

- Medline (Ovid) (1966-June 2006)
- Embase (1980-June 2006)
- NHS Economic Evaluations Database (NHS EED)
- PsycINFO
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)

The electronic search strategies were developed in Medline and adapted for use with the other information databases. The clinical search strategy was supplemented with economic search terms. Titles and abstracts retrieved were subjected to an inclusion/exclusion criterion and relevant papers were ordered. No criteria for study design were imposed a priori. In this way the searches were not constrained to randomised controlled trials (RCTs) containing formal economic evaluations. Papers were included if they were:

- Full/partial economic evaluations
- Written in English, and reported health economic information that could be generalised to UK.

Included papers were critically appraised by a health economist using the quality and applicability checklist outlined in the NICE guidelines manual. If a paper was included, costs, outcomes and a description of its quality and applicability were presented in the economic evidence table with a brief description.

Each economic study was categorised as one of the following types of full economic evaluation: cost-effectiveness analysis, cost-utility analysis (i.e. cost-effectiveness analysis with effectiveness measured in terms of QALYs gained) or cost-minimisation analysis. Other studies which did not provide an overall measure of health gain or attempt to synthesise costs and benefits were categorised as 'cost-consequence analysis.' Such studies were considered partial economic evaluations.

3.10.2 Cost-effectiveness modelling methods

Following a review of the economic literature, the GDG agreed on a priority area for original health economic modelling for the guideline. The analysis undertaken assessed the relative cost-effectiveness of different intervention sequences compared to one another and to no treatment. A summary of economic model results are presented in relevant guideline chapters and the details of the economic model are described in Appendix G.

3.11 Development of the recommendations

In preparation for each meeting, the following papers were made available to the GDG one week before the scheduled GDG meeting:

- The protocol followed in terms of the methods of the evidence review.
- Summary of the clinical evidence and quality (as presented in the chapters)
- Extractions of the clinical and economic evidence (when possible)

The GDG discussed the evidence at the meeting and agreed evidence statements and recommendations.

The GDG then developed care pathway algorithms according to the recommendations.

3.12 Areas without evidence and consensus methodology

The table of clinical questions in Appendix B indicates which questions were searched.

In cases where evidence was sparse, the GDG derived the recommendations via informal consensus methods, using extrapolated evidence where appropriate. All details of how the recommendations were derived can be seen in the 'Evidence to recommendations' section of each of the chapters.

3.13 Update

This guideline will be updated when appropriate. The decision to update will balance the need to reflect changes in the evidence against the need for stability, as frequent changes to the recommendations would make implementation difficult. We check for new evidence three years after publication, to decide whether all or part of the guideline should be updated. In exceptional circumstances, if important new evidence is published at other times, we may conduct a more rapid update of some recommendations. Any update will follow the methodology outlined in the NICE guidelines manual.

3.14 Consultation

The guideline has been developed in accordance with the Institute's guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline and the draft of the full and short form guideline. In addition, the draft was reviewed by an independent Guideline Review Panel (GRP) established by the Institute.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented for consideration by the GDG. All comments were considered systematically by the GDG and the development team recorded the agreed responses.

3.15 Related NICE Guidance

Constipation: the diagnosis and management of idiopathic childhood constipation in primary and secondary care. Published May 2010.

When to suspect child maltreatment. NICE clinical guideline 89 (2009)

Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE clinical guideline 76 (2009).

3.16 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCGC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

3.17 Funding

The NCGC was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

4 Impact of bedwetting on children and young people and their families

4.1 Introduction

Three themes were identified in the evidence review in this area: studies of the impact of nocturnal enuresis on children's self-esteem and self-image; studies whose aim was to elicit views and attitudes from children and their families regarding nocturnal enuresis; and studies which examined the association between bedwetting and domestic violence.

4.2 What is the family impact of children and young people aged under 19 who have bedwetting?

4.2.1 Evidence review

4.2.2 Impact on self-esteem, self-concept and self-image

Several qualitative based studies were identified which considered the impact of nocturnal enuresis on children's self esteem. Self esteem has been studied in psychological research, mainly due to the correlation between low self-esteem and later mental health problems⁶⁵. However, it is an ill-defined concept particularly due to the interchangeable terminology and similar concepts such as self-concept, self-image and self-worth¹²⁹. Consequently, there are problems with the interpretation and comparison of research findings.

Butler and Green (1998) define self-construing as an *"internal" assessment of the way in which children feel and view themselves and the world in which they live*. The authors consider *self-image* as a descriptive feature of self, essentially how the child thinks about him or herself, whilst *self-esteem* is akin to an evaluation and how the child feels about him or herself.

4.2.2.1 Study characteristics

Theunis (2002)¹⁴⁸ conducted a quasi-experimental study in a group of 27 boys and 23 girls, who were treatment resistant. The mean age was 9 years and 10 months. Some of the children also had day-time and night-time incontinence. The type and severity of the nocturnal enuresis was not stated, and almost one fourth of the patients had combined diurnal and nocturnal problems. They were compared to 77 children of the same age without nocturnal enuresis. The mean age was 9 years and 7 months.

The instrument chosen to measure the perceived competence of the children on specific domains of their life was the Dutch translation and also validation of the “Self-Perception Profile for Children”.

Children with nocturnal enuresis were reported to have significantly lower global self-esteem ($p < 0.01$) and physical appearance ($p < 0.05$) than children without nocturnal enuresis.

There was a trend to a lower perceived competence in enuretic children concerning their scholastic skills and social acceptance, but it was not significant.

Enuretic girls had a significantly lower ($p < 0.01$) perceived competence than enuretic boys. There was also an interaction effect between study-group and gender, in terms of scholastic skills ($p < 0.01$), behavioural conduct ($p < 0.01$) and social acceptance ($p < 0.05$). The enuretic girls have the lower perceived competence and the non-enuretic girls the highest. In terms of behavioural conduct, the enuretic boys had the highest perceived competence and non-enuretic boys the lowest.

Regarding social acceptance ($p < 0.05$), physical appearance ($p < 0.05$) and global self-esteem ($p < 0.05$), the 10-12 year old enuretic children had the lower perceived competence and the 10-12 years old non-enuretic children had the highest perceived competence. This was also present in terms of the children’s scholastic skills ($p < 0.05$) and behavioural conduct ($p < 0.05$). The 10-12 years old enuretic children had the lowest perceived competence and the 8-9 years old enuretic children had the highest perceived competence.

Butler (2007)²⁰ sent a questionnaire to 10985 children with a 74.7% response rate, who were part of the Avon Longitudinal Study of Parents and Children (ALSPAC). The sample comprised 4012 (48.0%) male and 4197 (51.1%) female. The bedwetting data was retrieved from a questionnaire administered to parents when their study child was 9 years of age. The mean age at completion was 115.8 months.

Among the children, 36.7% considered wetting the bed as really difficult, and was ranked eighth out of twenty-one behind events of a social and schooling nature. Overall, children with bedwetting appear to construe childhood difficulties in a very similar way to those who do not wet the bed. Dissatisfaction with appearance was also significantly more difficult. Those with nocturnal enuresis construed wetting the bed as significantly more difficult. Boys were significantly more likely to view bed-wetting as a more difficult problem for children than girls did..

Hagglof (1996)⁶⁵ and **Hagglof (1998)**⁶⁶ conducted a study of self-esteem before and after medical treatment in children with primary nocturnal enuresis (NE) and urinary incontinence (UI) in Sweden. One hundred and eleven children participated in the study, and 64 healthy children without any NEUI symptoms were recruited as controls. Among the children with NEUI, 25 had primary NE, 13 primary UI, 22 had a combination of both. Six children had secondary urinary dysfunction. Two questionnaires were given to the parents, and a clinical examination and psychological test were performed. Self-esteem was measured using the Swedish self-esteem inventory "I think I am". Children with NE received either an enuresis alarm or desmopressin while the UI children received specific training programs focusing on regular voiding habits.

Children in the NEUI group scored significantly lower than controls in terms of mental health ($p < 0.001$), skills ($p < 0.01$), relation to parents ($p < 0.05$) and relation to others ($p < 0.001$), but not for body image. Additionally, it was shown that children with primary day NEUI had the lowest self-esteem scores (10.1), followed by combined primary day and night (11.9), primary night (13.4) and secondary NEUI (16.0). Despite not being significant, a tendency was found for boys to have lower self-esteem scores than girls ($p < 0.08$) and NEUI children from lower socio-economic groups had lower scores than children from higher socio-economic groups ($p < 0.1$).

Children with secondary forms had the highest (which were still below normal), while those with primary day-time incontinence had the lowest self-esteem scores.

After 6 months treatment, NEUI children that had become completely dry (for at least one month) had significantly higher self-esteem scores compared to children with persisting NEUI (mean 23.1 and 17.3, respectively, $p < 0.001$).

Collier (2002)³⁶ collected data as part of a 2.5 year longitudinal study to assess nocturnal enuresis in children aged 6-16 year who presented to 15 community enuresis clinics. One hundred and fourteen children were enrolled into the study. There were 72 boys with a median age of 9.00 years and 42 girls with a median age of 9.5 years. Children had to be aged over 7 years; wetting at least 1 night a week; have a normal clinical examination and no neurological or urological cause for the enuresis; and parental and child consent to participate in the study. Clinical details; information regarding onset of wetting; number of wet nights; extent of wetting; and presence of urinary tract infections were recorded. Children also completed the Butler Self-Image Profile and the Coopersmith Self-Esteem inventory.

Girls had significantly higher scores ($p = 0.008$) on positive self-image compared to boys. Those with secondary enuresis also scored higher on positive self-image compared with those with primary nocturnal enuresis ($p = 0.02$). Severity of wetting was statistically associated with negative self-image scores ($p = 0.01$). However the

authors pointed out that this was not a clinically meaningful relationship, as less than 7% of the variance of self-image scores could be attributed to the severity of the wetting.

Robinson (2003)¹²⁹ measured different aspects of self-construing in children aged between 7 to 16 years with primary mono-symptomatic nocturnal enuresis. This study was conducted in England. To be included children also had to wet the bed at least three times a week; to not be on any treatment; not have daytime wetting; not have any urological nor neurological cause for the enuresis; and attend mainstream education. Children with nocturnal enuresis were recruited from a paediatric outpatient's clinic and the control group was randomly selected from one primary and secondary school.

Children were given the Self-Image Profile, the Coopersmith Self-Esteem Inventory and the "I think I am", which was translated from Swedish to English.

The authors found that the only significant difference ($p=0.011$) was the tendency for children with primary monosymptomatic nocturnal enuresis to construe themselves more negatively on the Butler Self Image Profile (SIP) when compared to a matched control group. No significant differences were found on self-esteem, self-identity or positive self-image.

Pugner (1997)¹²² conducted a study to evaluate the costs of nocturnal enuresis to the health care system and families in 5 European countries. The authors only presented the results from 3 of these countries (Sweden, United Kingdom and Germany). To estimate typical consultation costs of enuretic children, 11 hospital consultants and 15 primary care clinicians were interviewed across the 5 countries. The study used Butler's "self image profile" to assess self esteem in children.

The study showed that before children had treatment they reported feeling "different from others", "lonely" and "shy". The study suggested children with enuresis have a lower than average self esteem and suggests appropriate treatment is needed for children with nocturnal enuresis.

4.2.3 Children and Young People's views and attitudes on the impact of nocturnal enuresis

Several interview and survey based studies were identified which considered the impact of nocturnal enuresis on children with nocturnal enuresis. Some observational studies were also retrieved. The studies focused on the children's attitude to their bed wetting, the treatments and the success of treatments. The

studies also considered the concern, worry, and psychological problems caused by having nocturnal enuresis.

4.2.3.1 *Study characteristics*

Joinson (2007)⁷⁷ investigated the psychological problems associated with bedwetting and combined (day and night) wetting in children aged around 7.5 years. Based on the reports from parents and children, the study compared the rate of internalising and externalising problems and problems with bullying and friendships in children with bedwetting, combined wetting, and in children with no wetting problems. They collected both wetting and parent-reported data from 8,242 questionnaires distributed to a cohort enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC). Child reported psychological measures were taken from a clinic attended by 7,171 children (age range 97-125 months).

Children invited to attend a clinic, where interviewed using: a modified version of the Bullying and Friendship Interview Schedule; 11 items from the Self-Reported Antisocial Behaviour for Young Children Questionnaire; a reduced version of Harter's Self-Perception Profile for Children; and five questions from the Cambridge Hormones and Moods Project Friendship Questionnaire.

Even though the child-reported outcomes were much less evident to suggest differences between the groups than with the parent-reported outcomes (please see section 1.3.3.1), the study reported that children with combined wetting had an increased risk of antisocial activities. Overall, the study found a higher parent-reported psychological problems in children with bedwetting and combined wetting compared with those with no wetting problems.

Wagner (1986)¹⁶¹ collected self-report data from 100 enuretic children (n=61 male and n=39 female) between the ages of 5 and 14 (median 8.3 years). The study was conducted in the USA. Participants were recruited through the local paediatric clinics, private physicians, and newspaper advertisements for a behaviourally based enuresis treatment program provided by 3 university outpatient clinics. All children had primary nocturnal enuresis, wetting night-time only and wetting at least three nights per week.

The Child Attitude Scale for Nocturnal Enuresis was to understand how enuretic children viewed their problem. Parent ratings of the children's behavioural adjustment were obtained using the Behavioural Problem Checklist.

Older children (8-14 years) were less likely to indicate that they woke up right away when they wet their bed at night ($p < 0.02$). Children between the ages of 5 and 10 were less likely to report that their mothers made them take their sheets and wash

them ($p < 0.03$) compared to children of other ages. The youngest group (5-7 years) were most likely to report that their mothers would take responsibility for changing wet sheets in the morning ($p < 0.0001$).

Most children (65%) were unhappy about their wetting, and all indicated that they would be very happy if they could become dry. All also wanted to stop wetting their bed, but 14% were not willing to do anything to get dry. Most children (96%) felt they could stop wetting when they were older. Children reported that their fathers (97%) and mothers (99%) would be happy if the wetting stopped. Most children (84%) reported that other children did not make fun of them because they wet the bed, however 48% indicated that friends were aware of their bed wetting problem.

Wolanczyk (2002)¹⁶⁸ conducted a study to assess the impact of enuresis on children with a Polish version of the Child Attitude Toward Illness Scale (CATIS). The study included children seen at the Urodynamic Laboratory of the Mother and Child Institute in Warsaw, Poland who had nocturnal enuresis and / or diurnal enuresis. Children had a mean age of 12.74 (sd 2.51) years, 31 children were male, 32 children had primary nocturnal enuresis, 9 children had primary nocturnal enuresis and diurnal enuresis, 3 children had secondary nocturnal enuresis and 1 child had secondary nocturnal enuresis and diurnal enuresis. 16 children were wet every night or day.

The study used a Polish version of the CATIS to consider children with enuresis attitudes towards their nocturnal enuresis and compared these results to CATIS scores previously recorded of children with asthma and heart disease.

The study showed for children with enuresis there was no statistically significant relationship between the CATIS score and the age of the children. Girls had statistically significantly lower scores than boys ($p = 0.03$). The difference between older girls and boys was greater than between younger girls and boys. The study showed there was no statistically significant difference between children with nocturnal enuresis and children with diurnal enuresis.

The comparison of children with enuresis and children with asthma and heart disease showed children with enuresis had statistically significant lower scores than children with asthma and children with heart disease. There was no statistically significant difference between the scores of children with asthma and children with heart disease.

Morison (1998)¹⁰⁵ conducted interviews with 19 families and 20 young people to assess the experiences of “bed-wetting from the perspectives of young people their parents and siblings”. The study included young people aged 4 to 17 years in Scotland who were being treated by health care professionals for nocturnal enuresis.

To enable fair interviews for younger children, young children were asked to answer using a scale of faces.

The study divided the responses from the children in to 4 categories: acceptance and tolerance, ambivalence, proactive rejection and intolerance and resigned helplessness and hopelessness. Acceptance and tolerance was then subdivided in to primary unconcerned, happy, resigned pragmatic, optimistic pragmatic. Nearly all children in the study reported perceived helplessness and hopelessness which were identified as: repeated failures with treatment; unrewarded effort; the belief that most 3 year olds are able to be dry at night, making it look easy; and negative assessments of their bed-wetting by family and others.

Stromgren (1990)¹⁴² investigated whether young adults treated previously for nocturnal enuresis (mostly with a bed alarm) would display personality traits that could be related to the former enuresis and its treatment. In a 15 year follow up study, 25 of the 29 (14 girls and 15 boys) patients who were treated with a bed alarm as children (14 girls and 15 boys between 7-14 years old) and presumed to comprise all enuretic children in Samsø (Denmark), were compared for their personality profiles with fifteen healthy controls matched for age and sex. The first assessment revealed a conduct disorder in only one boy and no signs of psychiatric disorder were found in the children. In 11 of 29 cases, at least one of the parents had suffered from EN in childhood or adolescence. All children were found to respond in some degree to the treatment with bed alarm with 13 of them being fully recovered, and 13 exhibited less bed wetting. In a follow up study, the Karolinska Scales of Personality test was employed to assess responders' habitual feelings or behaviours when they were adults. Results from this study revealed that although adults being treated for EN as children did not hold conscious opposition or aggression towards their family home or the parents, they experience challenges on their adaptation to and belonging in society. More specifically, the two areas found to differentiate those who being treated for nocturnal enuresis in their childhood from healthy matched controls were socialization and suspicion. In relation to their socialization, the following areas were more significantly impacted; running away from home as a child, constantly getting into difficult situations, resistance to parents, problems at school (worry teachers and being reprimanded), got into trouble without being blamed, feeling of never had chance to get on in life, playing truant as a child. The area most affected in the breakdown of suspicion was the belief that other people were jealous of him/her

Morison (2000)¹⁰⁶ conducted a survey to assess the parents and young people beliefs about treatment and outcomes of nocturnal enuresis. The study used the "Family Perspective on Bed-Wetting Questionnaire (FPBWQ) to measure control beliefs and expected outcomes of treatment. The study followed up patients after 6

months of treatment. The study included 40 young people, 25 of which were male. The children had a mean age of 8 years, 95% wet the bed at least 3 nights a week and 60% wet the bed every night, 5% also had daytime wetting. The study stated that as only 5% of patients had day time wetting it reflected the practice of inviting only monosymptomatic children to community nurse-led clinics.

60% of children expressed concern about bedwetting, 40% replied they did not know to the question on concern about bed-wetting. 70% of parents believed the people who they felt were most important thought bed wetting should have stopped, with their parents opinion mattering most. 43% of children felt they could stop bedwetting. Most young people reported that effort was important in the success of a treatment, and 83% said they were willing to make the effort to become dry. The study reported the most children (68%) thought having the ability to become dry was important in success but only 38% said they thought they had the ability. 78% of children said they did not know what would help them to become dry. The study reported a high consistency between answered from children where they reported they “can” stop wetting the bed and are “able” to stop wetting the bed.

Schober (2004)¹³⁵ conducted a study of 110 children assessed attachment psychopathology on the AAQ angry distress scale and the care givers dissociation scores. The study included children who were seen during scheduled appointments at a pediatric urologist’s office or at a pediatric clinic. The study compared 50 children with monosymptomatic nocturnal enuresis to 60 children without nocturnal enuresis, the children had a mean age of 11.7 years. The monosymptomatic nocturnal enuresis group had 26 boys, compared to the non-enuresis group which had 21 boys. The study measured attachment psychopathology on the AAQ angry distress scale and the care givers dissociation scores.

The study showed children with nocturnal enuresis had significantly higher scores on the AAQ angry distress scale, showing greater psychopathology, compared to children without nocturnal enuresis. There was no statistically significant difference in the scores between females and males, or between those who were breast fed and those who weren’t. There was no statistically significant difference between those who were being cared for by biological parents and those cared for by a guardian, although the AAQ score were higher showing greater psychopathology for those cared for by a guardian.

Landgraf (2004)⁸⁸ conducted a survey in 5 sites across the USA. The survey received 208 responses. 56% were female; the children had an age range of 5 to 17 years. Fifty-four percent were wet at nights, 39.5% were wet during the night and day, 6.5% were wet during the day (3.8% was missing data). The questionnaires were mostly answered by the mothers of the children (88%). Fifty-four percent reported

that their child wet at night only compared to those for whom both daytime and nighttime wetting were indicated (40%). Isolated day-time wetting was indicated in 7% of the sample. Sixty-nine percent of the parents reported that this was not their child's first visit to a doctor for wetting. The study used the Child Impact Scale and Family Impact Scale to interpret the results of the survey. The Child Impact scale consisted of 14 items, 10 of which were specific to enuresis and its impact on child's life during the past 4 weeks, with the remaining 4 being more general (e.g. "my child works to his/her potential"). The parent was asked to indicate the degree to which the statements/items reflected how life had been for his/her child during the past 4 weeks.

Statistically significant differences in Child Impact scores were observed for 4 attitude items: "wetting is a behavioral issue" ($p=0.019$); "there is a neurologic basis for wetting" ($p=0.05$); "my child will outgrow the problem" ($p=0.05$); and "I'm concerned my child has a serious medical issue" ($p=0.000$). There were statistically significant differences for whether the child urinated at bedtime ($p=0.029$); and for the number of pads used ($p=0.005$). A marked difference was found for those using ≥ 2 pads versus no pads ($p=0.004$) and versus use of a single pad ($p=0.005$). A higher scale score was observed on the Child Impact scale for established parents (68.48) compared to those whom the physician reported as new to their care (68.98; $p=0.013$). A higher and statistically significant difference ($p=0.039$) was also observed on the Child Impact scale for girls (67.53) versus boys (63.99).

Van Tijen (1998)¹⁵⁷ explored the perceived stress of nocturnal enuresis in childhood and adolescence through the patient's severity rating of nocturnal enuresis in relation to other critical life events. This was a questionnaire based study of 98 children with NE and 124 controls, aged 8-18 years. The sample was divided in two age groups; one group was consisted of those aged 8-12 years and the other group of adolescents aged 12-18 years. Participants in the study were presented with the Critical Life Events Picture Test (CLEPT), a test designed for this study to investigate the child's perception of NE compared to 10 other critical events; divorce, strident parental fights, being teased, being excluded from the group, moving house, undergoing surgery, academic attainment, having little money to spend, being extremely short and having to wear glasses. For bed wetters, the severity of nocturnal enuresis was scored third in relation to its psychological impact by the primary school children, after divorce and parental fights and second with parental fights by adolescents. On the opposite, the controls did not attribute major importance to nocturnal enuresis.

4.2.4 Family / careers views and attitudes on the impact of nocturnal enuresis on children and young people

Several interview and survey based studies were identified which considered the impact of nocturnal enuresis on parents, carers and the family of children with nocturnal enuresis. The studies focused on the parent's and carer's attitude to the child and their bed wetting, the concern and worry caused by the child having nocturnal enuresis and the parental intolerance to the condition.

4.2.4.1 Study characteristics

De Bryune (2009)³⁹ assessed whether parental stress was related to behaviour in children between the ages of 6 and 12 years with nonmonosymptomatic nocturnal enuresis (NME). Children were diagnosed with NME using a 14 day diary and noninvasive standardized screening and if applicable by daytime incontinence according to ICCS terminology. A total of 47 boys (60.3%) and 31 girls (39.7%) with a mean \pm SD age of 8.42 ± 1.91 years (range 5 to 13 years) were recruited. The control group consisted of 110 children from a regular primary school. Children with enuresis were excluded from this group. The control group consisted of 56 boys (50.9%) and 54 girls (49.1%) with a mean age of 9.07 ± 1.93 years (range 5 to 12 years). Children were compared using the Child Behaviour Checklist (CBCL), the Disruptive Behaviour Disorders Rating Scale (DBDRS). Parental stress was measured with the Parenting Stress Index (PSI).

On the CBCL, mothers judged their children with NME as more withdrawn ($p=0.03$); more aggressive ($p=0.002$); and more inattentive ($p=0.01$) than mothers of the control group. Also, mothers of the study group reported significantly higher scores on the externalising ($p=0.01$) and total problem broadband scale ($p=0.004$). No significant differences between study and control groups were found in paternal reports. Maternal reports showed a significant effect of gender on child problem behaviour ($p \leq 0.01$) since mothers reported more attention problems in boys than in girls ($p \leq 0.05$).

Children of parents of children with NME showed higher scores on the DBDRS subscales inattention, hyperactivity/impulsivity and oppositional defiant disorder than those of parents of nonenuretic children.

Parental reports showed a significant main effect of gender since mothers and fathers reported more attention problems in boys ($p \leq 0.05$). A lower SES was associated with higher scores on conduct disorder ($p \leq 0.01$).

A significant group difference was found on all 3 PSI scales. Children of parents of children with NME showed significantly higher stress scores on the parental and child characteristics domains, and total stress index than parents of nonenuretic children. Mothers of boys showed higher stress scores on the child characteristics domain than mothers of girls ($p \leq 0.01$). Paternal reports did not show a significant gender effect.

Joinson (2007)⁷⁷ investigated the psychological problems associated with bedwetting and combined (day and night) wetting in children aged around 7.5 years. They collected both wetting and parent-reported data from 8,242 questionnaires distributed to a cohort enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC). The rates of psychological problems were compared in children with bedwetting, combined wetting, and in children with no wetting problems. The self-report questionnaire given to parents beyond several question on the child's wetting also included "The Development and Well-Being Assessment", comprising questions related to internalising and externalising disorder in children occurring in the present and recent past. The study found a higher rate of parent-reported psychological problems in children with bedwetting and combined wetting compared with those with no wetting problems. This was evident for most outcomes, particularly attention/activity problems, oppositional behaviour, and conduct problems. The exception was social fears and sadness/depression where the combined group were at no greater risk than the controls but rates of these problems were elevated in children who suffered from bedwetting alone. Children with combined wetting were particularly at risk for externalizing problems.

Wagner (1986)¹⁶¹ collected self-report data from 100 enuretic children (n=61 male and n=39 female) between the ages of 5 and 14 (median 8.3 years). The study was conducted in the USA. Participants were recruited through the local paediatric clinics, private physicians, and newspaper advertisements for a behaviourally based enuresis treatment program provided by 3 university outpatient clinics. All children had primary nocturnal enuresis, wetting night-time only and wetting at least three nights per week.

The Child Attitude Scale for Nocturnal Enuresis was to understand how enuretic children viewed their problem. Parent ratings of the children's behavioural adjustment were obtained using the Behavioural Problem Checklist.

The study showed most parents (77% of fathers and 75% of mothers) believed their child could become dry if they really wanted to. Most parents did not get angry at their child for wetting the bed (77% of fathers and 66% of mothers). These differences (between mothers and fathers) were not significantly difference although the study reports there was a trend for mothers to be angry more often than fathers were with the child wetting the bed.

Foxman (1986)⁶¹ described the impact of nocturnal enuresis on children as perceived by the parents. This description was based on the Rand Health Insurance Experiment, a US large population based study which considered the prevalence,

perceived impact and treatments available for children with nocturnal enuresis. The study included 2756 families and enrolled 7706 individuals, 70% were followed for 3 years and 30% for 5 years. Families were included if they earned less than \$54,000 per year, were not eligible for medicare. The study was conducted in six towns in the USA: Dayton, OH; Seattle, WA; Fitchburg and Leominster, MA; Franklin county, MA; Charleston, SC and Georgetown County, SC. The Rand Health Insurance Experiment conducted a questionnaire between 1975 and 1976. As part of the questionnaire the parents were asked one question about the impact of nocturnal enuresis on themselves: “during the past 3 months, how much has this child’s enuresis worried or concerned you?”

The question was answered on a scale of 1 to 4, with 1 being “none at all” and 4 being “a great deal”. The result of the question showed for parental concern 17% worried “a great deal”, 46% “some or a little” and 38% said it did not concern them at all.

Morison (1998)¹⁰⁵ conducted interviews with 19 families and 20 young people to assess the experiences of “bed-wetting from the perspectives of young people their parents and siblings”. The study included young people aged 4 to 17 years in Scotland who were being treated by health care professionals for nocturnal enuresis. To enable fair interviews for younger children, young children were asked to answer using a scale of faces.

The study divided the responses from the parents in to 3 categories: acceptance and tolerance, ambivalence and rejection and intolerance. The study showed parents whose overall attitude was “acceptance and tolerance” believed the child was helpless stating the child could not control their bladder at night. “Acceptance and tolerance” was described as the parents were willing to help their child become dry at night unless they knew that due to pathological reasons the child would never become dry at night. However within this group of parents there were different forms of acceptance and tolerance, those who had primary “unconditional acceptance and tolerance” where parents believed they could not help the child at the present time but the situation would change with time. “Transitional acceptance and tolerance” where the parent believes the situation will change soon. “Resigned acceptance and tolerance” where the parent believes the situation can not change. And “optimistic acceptance and tolerance” where the parent believes the situation will soon change for the better.

The study also showed some parents had an “ambivalent” attitude towards bedwetting where they believed the bed-wetting situation could only be changed by the child themselves. Parents who had “rejection and intolerance” where the

parent's believed the bed-wetting was within the child's control and therefore demonstrated frustration and anger in relation to the bed-wetting.

Morison (2000)¹⁰⁶ conducted a survey to assess the parents and young people beliefs about treatment and outcomes of nocturnal enuresis. The study used the "Family Perspective on Bed-Wetting Questionnaire (FPBWQ) to measure control beliefs and expected outcomes of treatment. The study followed up patients after 6 months of treatment. The study included 40 young people, 25 of which were male. The children had a mean age of 8 years, 95% wet the bed at least 3 nights a week and 60% wet the bed every night, 5% also had daytime wetting. The study stated that as only 5% of patients had day time wetting it reflected the practice of inviting only monosymptomatic children to community nurse-led clinics.

Most parents expressed concern about the bed wetting, 57% of parents believed the people who they felt were most important thought bed wetting should have stopped. The study compared the parent's responses to the child's response and showed parents were more optimistic than the child about the child's ability to become dry. 43% of parents reported their child was not trying hard enough to become dry, and at the 6 month follow up the relationship between this and the child failing treatment was significant ($p = 0.027$).

16% of parents reported they were too busy to help their child with the treatments for nocturnal enuresis. The study reported that if parents made more time available to help their children there maybe fewer early drop outs. 75% of parents said they felt healthcare professionals would be able to help their child become dry but 27% felt healthcare professionals who had previously treated their child were running out of methods to treat their child.

Schober (2004)¹³⁵ conducted a study of 110 children assessed attachment psychopathology on the AAQ angry distress scale and the care givers dissociation scores. The study included children who were seen during scheduled appointments at a pediatric urologist's office or at a pediatric clinic. The study compared 50 children with monosymptomatic nocturnal enuresis to 60 children without nocturnal enuresis, the children had a mean age of 11.7 years. The monosymptomatic nocturnal enuresis group had 26 boys, compared to the non-enuresis group which had 21 boys. The study measured attachment psychopathology on the AAQ angry distress scale and the care givers dissociation scores.

The study showed there was no statistically significant difference in the care givers dissociation scores between carers of children with nocturnal enuresis (5.82 sd 5.74) and carers children without nocturnal enuresis (3.71 sd 3.85).

Landgraf (2004)⁸⁸ conducted a survey in 5 sites across the USA. The survey received 208 responses. 56% were female; the children had an age range of 5 to 17 years. Fifty-four percent were wet at nights, 39.5% were wet during the night and day, 6.5% were wet during the day (3.8% was missing data). The questionnaires were mostly answered by the mothers of the children (88%). Fifty-four percent reported that their child wet at night only compared to those for whom both daytime and nighttime wetting were indicated (40%). Isolated day-time wetting was indicated in 7% of the sample. Sixty-nine percent of the parents reported that this was not their child's first visit to a doctor for wetting. The study used the Child Impact Scale and Family Impact Scale to interpret the results of the survey. The Family Impact scale included 17 items. The parent was asked to indicate how strongly each statement/item reflected the situation for them personally, at home, and with their family. All items were tailored to assess impact of enuresis on family relationships and activities (e.g. "relatives and family members are patient and tolerant about the problem").

There were statistically significant differences on the Parent Impact scale for all 6 of the global items (child ability to cope; family frustration; how often success was experienced; child commitment; family cohesion; and treatment success in past 4 weeks) with the p values ranging from 0.021 to 0.000. Differences were significant for 5 of the 7 attitude statements (child could control if tried harder; wetting problem a behavioral issue; having a neurological basis for wetting; wetting being a significant health problem; and being concerned that the child had a serious medical issue). The p values ranged from 0.026 to 0.001.

There were also statistically significant differences on the Parent Impact scale for whether the child urinated at bedtime ($p=0.002$); and for the number of pads used ($p=0.011$). A marked difference was found for those using ≥ 2 pads versus no pads ($p=0.003$) and versus use of a single pad ($p=0.012$).

Parental perceptions of nocturnal enuresis were explored in a collaborative study of 1379 children aged 4 years or older who were patients in nine medical centres in USA (Haque et al, 1981). One in four children (25.1%) was found to be enuretic. Each medical centre served the urban poor, although some centres had as much as 25% middle class population. The majority of population were blacks (57%), 27% white and the remainder mostly Hispanics. The vast majority (87%) of parents answering the questionnaires were mothers. Child's age of expected dryness differed significantly between parents of children with EN (mean age 3.18 years) and parents of children without EN (2.61 years). It seemed that the experiences of parents of bed wetters led them to allow more latitude in their expectations for achieving dryness. However, bed wetting was expressed as a problem by the large majority of both groups (61%) with the less educated parents being more worried and troubled about

bed wetting and its associated effects compared to more educated parents. Parental educational level was also related to the management of bed wetting; parents with only a school grade education punished more and sought more often medical advice about their children's bed wetting problem than the parents with higher education. On the contrast, parental educational level was not related to beliefs about bed wetting causes. More than one third of parents of both groups considered that enuresis has an emotional cause, with physical causes being ranked lower than emotional causes or heavy sleeping. Lastly, more than half of the parents failed to seek help from physicians at any time in the past, something that may resulted from lack of confidence in the physician's ability to solve the problem or lack of desire to deal with enuresis.

Chao (1997)³⁵ addressed the parental perspectives of primary monosymptomatic nocturnal enuresis (PMNE) as part of a multi-centre clinical trial on the use of oral desmopressin for the treatment of PMNE in children conducted in Singapore. Thirty patients were studied. Inclusion criteria was: age ranging from 7 to 16 years; present frequent bedwetting of at least 6 nights out of 2 weeks prior to the study; and absence of diurnal incontinence and urinary tract infection (excluded by urine culture).

Screening questionnaires were used during history taking in the initial clinic visits from parents and answers were recorded by the paediatricians on a one-to-one basis.

Patients had a mean age of 10.1 years, and there were 17 male and 13 females. Chinese ethnicity was predominant (70%), followed by 20% Indians, 6.7% Malays and 3.3% Eurasian. Seventeen (56.7%) patients had a family history of PMNE with 6 (35.5%) of them having 2 or more family members being affected.

Fifty percent of parents felt that PMNE was due to a maturational delay and another 50% of them thought that it was caused by deep sleep in the child who was unable to wake up to void. Thirteen (43.3%) parents felt that the problem was familial and 43.3% felt that it was due to behavioural problems in the child-being lazy, difficult or defiant. Eight (26.7%) parents blamed excessive fluid intake at night. Ninety percent of parent sought medical treatment because of restrictions on outdoor activities and twenty-six (86.7%) wanted a break from the constant laundry and cleaning of the aftermath. Fourteen parents (46.7%) sought treatment because of disrupted sleep for the household. PMNE was seen as a social stigma in 83.3% of patients.

4.2.5 Domestic violence against children and young people with nocturnal enuresis

Two retrieved studies examined the association between bedwetting and punishment and domestic violence.

Sapi (2009)¹³³ conducted a descriptive study involving 149 patients aged from 6 to 18 years (mean age 9.1±3.8), that described the frequency of domestic violence associated with episodes or urine leakage in children with primary monosymptomatic nocturnal enuresis (PMNE) and to describe the associated risk factors. Patients aged from 10 to 19 years were considered adolescents according to the classification of the WHO. PMNE was defined according to the International Children's Continence Society. Patients attended the pediatric outpatient clinical or the Centre of Study on Adolescent Health in Rio de Janeiro, Brazil, for a routine appointment with a pediatric urologist. After the medical visit, patients with PMNE were invited to participate in the study.

A semi-structured interview was administered by medical students involved in undergraduate scientific research and by pediatric urologists. At a first stage, the interview was done with the child or adolescent while one or more guardians were present. Subsequently, the instrument was given to the patient alone in an environment amenable to the playful activities. During this phase, data related to domestic relationships, circumstances and characteristics of the domestic violence and people involved in the aggressive events were collected. Patients were asked to provide the following data: age, degree of kinship and education level of the people who lived with the patients. Abusers were also identified. Punishment due to urinary incontinence was analysed regarding frequency and type, and was defined as: verbal; physical punishment without physical contact; and physical punishment with physical contact.

The sample had a frequency of 59.7% (n=89) of boys and 40.3% (n=60) of girls. There was not a significant association between sex and incidence of punishment due to episodes of nocturnal incontinence (p=0.544).

The presence of aggression aimed at punishing was detected in 132 patients (88.6%), and in all these cases there was verbal punishment. Physical punishment without physical contact (e.g. forced to take a cold shower, to wash up the wet sheets, to stand up for the rest of the night) occurred in 50.8% (n=67) of the cases, while physical punishment with physical contact account for 48.5% (n=64) of the cases.

The rate of violence with physical contact was significantly higher against children than adolescents (p=0.001; RR=1.31; 95%CI 1.12-1.52). The main abuser was the mother (87.9%), and in 14.4% of the cases, the aggression involved more than one

person who lived with the patient. In 88.4% of the cases, there were daily aggressive events.

One child had a severe genital lesion caused by burning, and a reconstructive surgery was needed to restore genital integrity.

The study reported that there was a significant correlation ($p=0.043$, $r=-0.768$) between the guardians' educational level and punishment severity. Patients who lived with low-educated abusers (less than 8 years of schooling) were victims of a higher rate of punishment with physical contact. All guardians reported their dissatisfaction regarding the patient's episodes or urine leakage.

A cross-sectional study conducted by **Can (2004)**³³ in Turkey in the 5-17 years age group included at least 600 children. A face-to-face interview of 889 mother was carried out. In the questionnaire, the existence, frequency and risk factors of enuresis were questioned in detail and the parental reactions to the child's enuresis were also assessed. The prevalence of nocturnal enuresis was 17.9% ($n=159$). Of 154 mothers, 11.7% ($n=18$) offered psychological support to their child and tried to find a solution to the problem. It was also found that from 133 interviewed mothers, 42.1% of the children were spanked, 40.6% of the children suffered neglect, 12.8% were beaten and 4.5% suffered swaddling. It was also found that the sex of the child ($p=0.660$) and the educational level of mothers ($p=0.435$) were not significant factors.

4.2.6 Economic evidence

The economic literature identified one study which aimed to assess the financial impact of nocturnal enuresis on the health service and families. The study was not a full economic evaluation and therefore was assessed as not applicable and as having very serious limitations. However, its focus on the costs to the family of different treatment strategies compared to one another and to no treatment was considered useful to explore important monetary impacts of bedwetting and treatment on the family.

4.2.6.1 Study characteristics

Pugner (1997)¹²² conducted a study to evaluate the costs of nocturnal enuresis to the health care system and families in 5 European countries. The authors only present the results from 3 of these countries (Sweden, United Kingdom and Germany). To estimate typical consultation costs of enuretic children, 11 hospital consultants and 15 primary care clinicians were interviewed across the 5 countries. They were asked about their individual approaches to management in the first 12 months from commencing treatment.

To assess the family costs associated with enuresis, 19 children with primary nocturnal enuresis (aged 6-12 years) were selected for inclusion by leading experts in the field. At enrollment, 6 of the children were using an enuresis alarm, 6 were receiving treatment with desmopressin and 7 were receiving no treatment or were using diapers. Parents completed a questionnaire designed to identify direct and indirect costs to the family as a consequence of their child's enuresis. Direct costs included expenditure on washing and drying, extra bed clothes, underwear, pyjamas and mattresses as well as travel costs to consultations. Indirect costs included time spent performing extra housework and consultation visits that prevented the carer from pursuing other activities. Also included was any external help required during periods when the carer was ill.

Three case studies were conducted in the UK. Of these, one child was treated with desmopressin spray, one child used an enuresis alarm and one received no treatment. 3-month costs to the health service and families are presented. Use of an alarm generated the greatest overall costs (£570), because there was no reduction in the number of wet nights after treatment initiation. 79% of these costs were borne directly or indirectly by the family. Because the child continued to wet 7 nights per week, even with alarm treatment, there was a high level of washing and drying. The alarm was also purchased directly by the family. A much lower cost for the family can be expected where the alarm is used successfully. The child receiving desmopressin incurred moderate costs (£255), 96% of which were costs to the National Health Service. The family costs amounted to £9 of direct expenditure because the treatment was successful at achieving complete dryness. The child receiving no treatment for his enuresis wet the bed infrequently (once per week) and thus incurred relatively low costs (£179), 32% of which was borne by the family. A child who wet the bed most nights would likely show an increased impact on the family economy.

The case studies from Sweden and Germany showed similar results. For patients undergoing treatment with an enuresis alarm, families bore just over half of all costs, around 51%. For patients being treated with desmopressin, between 72 and 96% of costs were borne by the health service. Finally, among patients not undergoing treatment, families paid about 80% of all costs, mostly in the form of washing and drying. In one Swedish case study, the family using diapers whilst waiting for treatment incurred low costs as no washing or drying was necessary.

The case studies demonstrate the importance of dryness in monetary terms for the family. Factors influencing the costs of enuresis include the number of wet nights per week that lead to washing and drying and the costs of treatment itself. In those case studies where the child has more than three wet nights per week, the 'no treatment' option represents the greatest cost burden to the family. Also, treatment

with an enuresis alarm requires a high degree of motivation from the family and the child and significant costs continue to be placed on the family as the child gradually improves. Finally, because treatment with desmopressin has an immediate effect in those who respond, costs borne by the family are dramatically reduced.

4.2.7 Evidence statements

Theunis (2002)¹⁴⁸; Hagglof (1997)⁶⁵

- One quasi-experimental study found that children with bedwetting had lower self-esteem than non-bed wetting children however one controlled study found that becoming dry increased self-esteem.
- One quasi-experimental study found children with bedwetting reported lower satisfaction with his/her looks and another controlled study found they construed themselves more negatively on self-image.

Hagglof (1997)⁶⁵; Collier (2002)³⁶

- One controlled study found that children with primary day wetting had lower self esteem, followed by children with primary day and night wetting, then children with primary night wetting and then secondary wetting. A longitudinal study similarly found that children with secondary wetting had a higher positive self-image.

Joinson (2007)⁷⁷; Hagglof (1997)⁶⁵; De Bryune (2009)³⁹; Pugner (1997)¹²²; Schober (2004)¹³⁵;

- Two surveys of parents reported higher psychological problems in bed wetters, one of the surveys reported children to be more withdrawn, aggressive and inattentive. Children in one cost-evaluation study reported feeling different from others, lonely and shy. A controlled study found lower scores on mental health, skills and relations to parents and others. Another study found higher psychopathology scores.

Theunis (2002)¹⁴⁸

- Younger children with bedwetting (8-9 years) perceived their competence in scholastic skills and behavioural conduct as higher than 10-12 year olds.

Collier (2002)³⁶; Butler (2007)²⁹, Wolanczyk (2002)¹⁶⁸

- In one study (survey) girls with bedwetting had higher positive self-image scores than bed wetting boys, in another study (survey) boys viewed bed-

wetting as more difficult, and in another study girls had a more negative attitude towards bed wetting than boys (survey).

Morison (1998)¹⁰⁵

- In one interview study children reported perceived helplessness and hopelessness due to repeated treatment failure, unrewarded effort, belief that younger children could be dry at night and negative assessments from family and others.

Morison (2000)¹⁰⁶; **Wagner (1986)**¹⁶¹

- Children in one questionnaire study believed they could become dry when they are older and a survey of young people believed effort was important in treatment success and were willing to make the effort but were worried in their ability and most did not know what would make them dry. Most parents showed concern with bed wetting and in two surveys thought their child could become dry if they really wanted to, which in one study was significantly related to the child failing treatment.

Landgraf (2004)⁸⁸

- In one survey study most parents did not get angry because of bedwetting and in another study survey it was found that less educated parents were more likely to punish.

Sapi (2009)¹³³; **Can (2004)**³³

- In one qualitative study and one cross sectional study it was found that many of the parents used aggression to punish, often with physical punishment with or without physical contact and sometimes neglect. These studies took place in Turkey and Brazil.

4.2.8 Evidence to recommendations

Relative values of different outcomes

The findings of this evidence review were descriptive findings indicating the impact

of bedwetting on children and their families.

Trade off between clinical benefit and harms

Not relevant

Economic considerations

The cost impact of bedwetting on families can be considerable. The costs of doing additional laundry, buying extra linens and replacing mattresses are among the many extra costs families face in managing bedwetting. Children and their families also report bedwetting to have a negative impact on their overall quality of life. Seeking treatment for a child's bedwetting is likely to help to alleviate some of the financial burden and improve the quality of life for children and their parents and carers.

Cost-effectiveness modeling undertaken for the guideline indicates that from the perspective of the NHS, treating children with bedwetting is cost-effective compared to not treating. This conclusion applies to children commencing appropriate treatment at ages as young as 5 years. The GDG recognise that a recommendation to treat younger children, where appropriate, is likely to represent a considerable cost impact to the NHS, but they felt that this group could benefit from advice about fluids and toileting and potentially medical treatment. Quality of evidence (this includes clinical and economic)

The studies examining constructs such as self-esteem used a variety of different instruments and many instruments and questionnaires used had not been validated. The studies particularly those on punishment and violence were from non-UK settings which might not be directly relevant to the UK population.

Other considerations

The GDG considered that bedwetting and other wetting problems have an impact not only on the child with bedwetting but on all other members of the family. They considered that living with a child with bedwetting can have a considerable impact on family finances which is often not recognized and not including when costs and benefits of treatment are considered.

The GDG considered the following findings of the review particularly significant; bedwetting can affect a child's self esteem, can cause negative feelings and behaviours and can limit social opportunities during important periods of self development; bedwetting causes stress to parents/carers; a minority of parents/guardians punish their children for bedwetting, either verbally, or to a lesser extent, physically; self esteem scores increase following successful treatment; time commitment from parents has an effect upon treatment dropout; boys seem to rate bedwetting as more difficult than girls and boys have lower self esteem scores than girls; bedwetting has an effect upon the family's budget/economy

The following was written by one of the patient/carer members:

"From our as a family with experience of NE, one of the most significant paragraphs I read in this section was "Most children (65%) were unhappy about their wetting, and all indicated that they would be very happy if they could become dry. All also wanted to stop wetting their bed, but 14% were not willing to do anything to get dry. Most children (96%) felt they could stop wetting when they were older. Children reported that their fathers (97%) and mothers (99%) would be happy if the wetting stopped. Most children (84%) reported that other children did not make fun of them because they wet the bed, however 48% indicated that friends were aware of their bed wetting problem."Our son falls into the 14% who won't do anything to get dry (typical teenage boy!) although he does take desmopressin and would probably try acupuncture. He is also one of the 48% whose friends are aware.

I also believe the following paragraph is significant:" Sixteen percent of parents reported they were too busy to help their child with the treatments for nocturnal enuresis. The study reported that if parents made more time available to help their children there might be fewer early drop outs. Seventy five percent of parents said they felt healthcare professionals would be able to help their child become dry but 27% felt healthcare professionals who had previously treated their child were running out of methods to treat their child. "It raises the question about whether we as parents may be contributing to the number of treatment resistant children! This assumes a link between dropout and treatment resistance which may not be justified. Is Morrison's statement about the link between parental time and early drop out is a valid one? I am sure we are not unique in being a family with two children who have NE. The "double whammy" impact of this on children/families should not be underestimated in terms of emotional and financial costs"

The GDG wished to have a positive recommendation not to exclude children under the age of 7 from consideration of treatment. The impact on children and families may equally be felt in those under 7 years and these children are likely to benefit from advice about fluids and toileting and depending on the child may also be able to cope with alarm or medical treatment. The evidence reviews on interventions informed this recommendation but more specific recommendations about individual treatments for children under 7 are included in relevant chapters.

The GDG discussed whether it was appropriate to include the studies of domestic violence in the review. They considered that the definitions of domestic violence varied and that the practices described may be particular to the cultural contexts of the studies (one was conducted in Brazil and the other in Turkey). However the GDG reported seeing children from a wide variety of cultural backgrounds and that this was likely to be increasingly common given the multicultural nature of many areas of

England and Wales. Under these circumstances the GDG considered that health care professionals should be alert to possibility of maltreatment and agreed to include these reviews in the evidence considered. They decided therefore to cross refer to recommendations from the maltreatment guideline ('When to suspect child maltreatment', NICE clinical guideline 89). The GDG considered it vital that healthcare professionals explore with parents and carers how they were coping the impact of bedwetting and in particular that they be alert to anger and negativity directed towards the child. These need to be addressed in its own right but may also influence the choice of treatment as e.g. alarm treatment may be too onerous for some families.

4.2.9 Recommendations

- 4.2.9.1 *Inform children with bedwetting and their parents or carers that bedwetting is not the child's fault and that punitive measures should not be used in the management of bedwetting. [1.1.1]*
- 4.2.9.2 *Offer support, assessment and appropriate treatment to all children with bedwetting and their parents and carers tailored to the child's and parents' or carers' circumstances and needs. [1.1.2]*
- 4.2.9.3 *Do not exclude younger children (for example, those under 7 years) from the management of bedwetting on the basis of age alone. [1.1.3]*
- 4.2.9.4 *Offer information and details of support groups to children being treated for bedwetting and their parents and carers. [1.2.2]*
- 4.2.9.5 *Offer information about practical ways to reduce the impact of bedwetting before and during treatment (for example, using bed protection and washable and disposable products).[1.2.3]*
- 4.2.9.6 *Discuss with the child's parents or carers whether they need support, particularly if they are having difficulty coping with the burden of bedwetting, or if they are expressing anger, negativity or blame towards the child. [1.3.17]*
- 4.2.9.7 *Consider child maltreatment⁶ if:*
- *a child is reported to be deliberately bedwetting*
 - *parents or carers are seen or reported to punish a child for bedwetting despite professional advice that the symptom is involuntary*
 - *a child has secondary daytime wetting or secondary bedwetting that persists despite adequate assessment and management unless there is a medical explanation (for example, urinary tract infection) or clearly identified stressful situation that is not part of maltreatment (for example, bereavement, parental separation).[1.3.18]*

[This recommendation is adapted from 'When to suspect child maltreatment' (NICE clinical guideline 89).]

⁶ For the purposes of the child mistreatment guideline, to consider child maltreatment means that maltreatment is one possible explanation for the alerting feature or is included in the differential diagnosis.

5 Patient Choice in children and young people with bedwetting

5.1 Introduction

Management of bedwetting can require significant effort from child and family and offering choice and involvement in decisions may help engagement with treatments. The GDG were interested in whether there was any evidence particular to nocturnal enuresis in the literature.

5.2 *In children and young people with bedwetting, how does patient or parent/carer choice over treatment intervention influence treatment outcomes?*

5.2.1 Evidence review

The evidence review identified two studies in total. Studies were identified from both the original and complementary searches, 1 of which was observational trials. Full details of the study can be found in Appendix C, which contains the extractions of all the studies included in this evidence review. Below is a brief narrative description of the main findings of the evidence review.

Randomised Controlled Trials

Lottmann (2007)⁹³ conducted a 6 week, randomised, open-label, cross-over study in children and adolescents with monosymptomatic PNE. The main aim was to compare patient preference in 221 patients for sublingual desmopressin oral lyophilisate (MELT) compared to conventional tablet treatment. The secondary aims were to compare efficacy, safety and ease of use of each formulation, volume of water taken on each dosing occasion and compliance for each formula. The study was performed at 26 centres in several European countries. To be eligible, patients were aged 5 to 15 years, diagnosed with PNE, who were already receiving desmopressin tablets (for at least 2 weeks) at a dose of either 0.2 or 0.4mg (2x0.2mg). Patients were excluded if they were experiencing daytime urgency, frequency (>7 micturitions during daytime), voiding postponement, infrequency (<3 voidings during daytime), painful voiding, weak stream and/or day wetting (more than once per week), urological disease, diurnal urinary incontinence, diabetes insipidus, ongoing urinary tract infection or other clinically significant diseases. The

use of non-pharmacological therapy (e.g. bed alarms) for PNE during 60 days before the screening visit was not allowed for the study participants.

The study comprised a 2 week screening period, during which patients continued to receive stabilisation dose of desmopressin tablet; two 3 week treatment periods; and a post-study safety assessment 1-3 weeks after completion of the study.

Overall, the study presented a low level of bias. According to ITT analysis, 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.

Quasi-Experimental Studies

Diaz-Saldano (2007)⁴¹ conducted a nonrandomised study aimed to compare the effectiveness of treatment for primary nocturnal enuresis (PNE) using a physician advised treatment plan based on medical evaluation versus a parent chosen alternative treatment plan based on parent needs. The study included 119 children, 85 males and 34 females. The mean age (sd) was 10 ± 3 years.

PNE was defined as wetting at night during sleep during any 6 month interval without any known causative problem. Bedwetting was defined as >2 wet nights per week, and remission was defined as dry for 14 consecutive nights. Relapse was defined as bedwetting occurring twice weekly after being dry for 6 months, and cure was to be dry for 1 year or more. Exclusion criteria for this study were: 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.

The physician treatment plans 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. Seventy-six children were treated with this therapy.

The parent chosen plans 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. Forty-three children were treated with this therapy.

Time to PNE remission using physician advised treatment was significantly sooner than by 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%, $p < 0.00001$).

5.2.2 Evidence statements

Diaz-Saldano (2007) ⁴¹

- Evidence from one quasi-experimental study show no greater effectiveness for patient preferred treatment interventions for nocturnal enuresis.

Lottmann (2007) ⁹³

- Evidence from one open-label randomised controlled trial shows that patients aged <12 years preferred sublingual oral desmopressin to tablet treatment (60.6%; 95% CI: 52.6-68.2; and $p = 0.009$)

5.2.3 Evidence to recommendations

Relative values of different outcomes

The GDG were interested in trials assessing changes in outcomes according to whether or not children or their families had expressed choice in treatment. This type of study was not available.

Trade off between clinical benefit and harms

No evidence was identified of harms

Economic considerations

No economic evidence was identified, but the GDG considered that exploring and managing expectations for treatment was an essential part of ensuring success. Tailoring choice of treatment to the individual needs and expectations of the child and his/her carer will help to avoid the prescribing of inappropriate interventions and possible progression to other alternatives.

Quality of evidence (this includes clinical and economic)

The quality of the evidence was limited - one randomised trial included was of a selected population where all children had agreed to have one or the other type of desmopressin therefore it was possible this group did not have a strong preference for either treatment available.

Other considerations

Although the evidence does not suggest that patient choice has an impact on the effectiveness of treatment the GDG discussed the good practice of informing and discussing treatment options with patients and parents/carers to allow choice between different effective treatments. The GDG considered that there were important principles of care which included involving both the child and family and properly considering their views, explaining the treatments available are and their likelihood of success. The GDG acknowledged that the family may consider the child needs treatment but the child may not consider they do. Understanding the expectations of the child and family are important in tailoring information and the GDG considered it useful to know if short term effect was the priority when families consult. The GDG used these principles when considering advice to be given for each management strategy.

5.2.4 Recommendations

5.2.4.1 *Explain the condition, the effect and aims of treatment, and the pros and cons of proposed treatment to the child and parents or carers.[1.4.1]*

5.2.4.2 *Clarify what the child and parents or carers hope the treatment will achieve. Ask whether short-term dryness is a priority for family or recreational reasons (for example, for a sleep-over)[1.4.2].*

5.2.4.3 *Explore the child's views about their bedwetting, including:*

- *what the child thinks the main problem is*
- *whether the child thinks the problem needs treatment.[1.4.3]*

6 Assessment for children with Bedwetting

6.1 Introduction

This section presents the evidence outlining different assessment methods which may be considered for use in the assessment of children with bedwetting. The main aims of conducting an assessment are to establish the diagnosis; find out what parent/child wants, to rule out or identify underlying causes and to indentify the factors that will influence choice of management strategy.

6.2 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 bedwetting?

6.3 What are the core laboratory urine / blood tests in the evaluation of children and young people under 19 years old who have bedwetting?

6.4 Evidence review for assessment

The evidence review identified 34 studies in total. All were identified in the additional search that was conducted to identify observational studies relevant to the guideline clinical questions concerning different aspects of assessment. Full details of the studies can be found in Appendix C, which contains the extractions of all the studies included in this evidence review. Rather than provide a narrative account of the details of all studies, we have chosen to present the main features and findings of the studies for all clinical questions under the assessment section in tables.

6.4.1.1 Assessment

The tables below summarise the evidence found in the review:

Table 6-1: Assessment papers – populations studied and tests used:

Author	Test	Test details	Population
	Radiological		

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Van Der Vismelsen (1992) ¹⁵³	Urodynamics	Micturition, decreased bladder capacity, urine flow patterns, anatomical obstruction, functional disturbance, renography, vesico-renal reflux, dilated renal pelvis, parenchymal kidney damage, a-functional kidney	Treatment resistant children
Yeung (2004) ¹⁷¹	Urodynamics / ultrasound	Bladder wall thickness and bladder volume	Primary monosymptomatic NE
Redman (1979) ¹²⁵	Radiological	IVP or cystography	NE population
Cutler (1978) ³⁷	Radiographic	Intravenous pyelogram and voiding cystourethrogram	NE population, some also had diurnal enuresis
Yeung (1999) ¹⁷⁰	Cystometry	Daytime and night-time urinary output; functional bladder capacity	Monosymptomatic NE treatment resistant children
Sujka (1991) ¹⁴³	Cystourethrogram	Patients with reflux	NE population
Tanaka (2003) ¹⁴⁶	Reflux detection	VCUG, urological diseases, cystometry, intravenous pyelography or renal ultrasonography	NE population
Zink (2008) ¹⁷³	Radiological	A detailed history, paediatric 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	Monosymptomatic NE and non-monosymptomatic NE
	History		
Cayan (2001) ³⁴	Constipation	Diagnosis of constipation, by questionnaire, laboratory tests and physical examination	Primary monosymptomatic NE

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McGrath (2008) ¹⁰¹	Constipation	Questionnaire and clinical examination	Tertiary paediatric clinic
O'Regan (1986) ¹¹⁶	Constipation	Assessment and treatment for constipation	NE population
Butler (2004) ³²	3 Systems approach	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, wets soon after sleep; parents answered often or rarely to each sign	No major daytime wetting
Siegel (1976) ¹³⁸	Allergy, UTI	The number of children with persistent NE (night wetting every week) between children previously treated for UTI and children with allergies	Young children
Robson (2005) ¹³⁰	Characteristics	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	Primary and secondary NE
Nappo (2002) ¹⁰⁹	Characteristics	A questionnaire based on history, results of physical and diagnostic examinations and therapy	NE population
	Bladder Diaries		
Kwak (2008) ⁵²	Bladder diaries	Comparison of bladder diaries and non validates LUTS questionnaire	Treatment resistant children
	Psychological tests		
Van Hoacke (2004) ¹⁵⁵	Psychological test	Social anxiety scale for children, state trait anxiety inventory for children, shortened depression questionnaire for children, self perception scale for children	NE population

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Van Hoacke (2007) ¹⁵⁴	Psychological test	Internalising scale of CBCL, ADHD scales of DBDRS,	Monosymptomatic NE and non-monosymptomatic NE
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Table 6-2 : Main findings from studies listed in table 6-1 Assessment:

Author	Setting	Outcome	Prevalence	Impact on treatment
Radiological				
Van Der Vismensen (1992) ¹⁵³	Netherlands	% of children with radiographic abnormalities	No comparison group	Not reported
Yeung (2004) ¹⁷¹	Enuresis clinic, Hong Kong	Relationship between bladder wall thickness and bladder volume in response to desmopressin	Not reported	Children with a thicker bladder wall were less likely to respond to desmopressin; Children with a larger bladder volume were more likely to respond to desmopressin
Redman (1979) ¹²⁵	University Hospital, USA	Number of children with abnormalities	No comparison group	Not reported
Cutler (1978) ³⁷	Primary Medical Centre, USA	Radiographic abnormalities and surgery	No comparison group	Not reported
Yeung (1999) ¹⁷⁰	Hospital, China	Pattern of NE based on urodynamic findings	No comparison group	No clear trend in response to desmopressin
Sujka (1991) ¹⁴³	Department of Urology, Buffalo, USA	Patients with or without reflux	No statistically significant difference in characteristics between children with reflux and children without reflux	Not reported

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Tanaka (2003) ¹⁴⁶	Outpatient clinic, Japan	Rate of reflux between MNE and NMNE, prognosis after 2 years (treatment with anticholinergics)	A positive history of NE in siblings and frequency were both statistically more common in children with reflux	Children who responded to treatment showed no statistical difference in the number of children with or without reflux
Zink (2008) ¹⁷³	University Hospital, Germany	Differences in CBCL score, ICD-10 score, uroflow, ultrasound residual urine, bladder wall thickness	NMNE patients had statistically more residual urine and thicker bladder wall	Not reported
History				
Cayan (2001) ³⁴	Day care centres and schools, Turkey	Differences between MNE patients and controls	Statistically significantly more children with MNE had constipation	Not reported
McGrath (2008) ¹⁰¹	Clinic, Hospital, Australia	Number of children with constipation	Statistically more children who had failed treatment with an alarm were constipated; poor level of agreement between parental reporting of constipation and clinical results	Not reported
O'Regan (1986) ¹¹⁶	University, Canada	Impact of treatment of constipation	22 out of 25 children had constipation	Treatment for constipation lead to children becoming initially dry
Butler (2004) ³²	Outpatients for NE at Hospital, UK	Predictive factors in successful treatment with desmopressin or anticholinergics from the 3 systems approach	Not reported	No predictive factors for desmopressin; predictive factors for successful treatment with anticholinergics was: age, frequency, passing small voids, small or variable wet patches, wakes soon after voiding
Siegel (1976) ¹³⁸	USA	NE in UTI and allergy	There was no statistical difference between the	Not reported

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		patients	number of children with persistent NE (night wetting every week) between children previously treated for UTI and controls. There was no statistical difference between the number of children with persistent NE (night wetting every week) between children with allergies and controls	
Robson (2005) ¹³⁰	University Hospital, USA	Differences between PNE and SNE	Constipation statistically more prevalent in SNE	Not reported
Nappo (2002) ¹⁰⁹	Centres in Italy	% results of number of children with characteristics	No comparison group	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)
Bladder Diaries				
Kwak (2008) ⁸⁶	Hospital, Korea	Differences in bladder diaries and questionnaire	No similarities in the results of bladder diaries or questionnaire	Not reported
Psychological				

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Van Hoacke (2004) ¹⁵⁵	Paediatric urology / nephrologic Centre, Hospital, Belgium	Differences in scales and questionnaires	CBCL score: children with NE are more withdrawn and anxious / depressive; Other scores: children with NE had difference social desirability score	Not reported
Van Hoacke (2007) ¹⁵⁴	Tertiary care	Scores on CBCL, DBDRS scales, and sensitivity / specificity	No comparison group	Not reported

Table 6-3: Prediction papers - population studied and tests used:

Author	Test	Test Details	Population
	Radiological		
Persson (1993) ¹¹⁹	Urodynamic findings	Uninhibited bladder contractions, graduation of detrusor instability, reduced bladder capacity, extent of volume decrease, age and gender	NE population
	Investigations		
Evans (1992) ⁵³	Nocturnal Polyuria	Urine volumes, osmolalities, AVP concentrations	NE population
Eller (1998) ⁴⁹	Predictive Factors	voiding diaries, daytime functional bladder capacity and urine osmolality	Monosymptomatic NE
	History		
Kruse (1999) ⁸⁵	Daytime bladder dysfunction	Monitor amount and how often children void during the day, inform children to void every 2 or 3 hours and to drink regularly during the day	Treatment resistant children

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Devlin (1990) ⁴⁰	Patient characteristics	Sociodemographic data, enuresis history, physical / psychiatric disorder, family stress	NE population
Butler (1990) ³¹	Patient characteristics	Resistance constructs, perceived family support, perceive family intolerance, teased by siblings and secrecy of NE	NE population
Butler (1998) ²¹	Patient characteristics	Demographic, situational, enuresis history, physiological, parental attitude and child	Monosymptomatic NE
Kruse (2001) ⁸⁴	Predictive factors	Age, gender, family history, previous treatment, frequency of wetting	Monosymptomatic NE
Butler (1990) ²⁵	Pre-treatment variables	Pre treatment variables and relapse rates	NE population
Fielding (1985) ⁵⁷	Predictive factors	30 pre treatment variables - history and current status of enuresis, family history of enuresis, social background and other behaviour problems	Children with night only wetting, children with night and day wetting
Dische (1983) ⁴³	Predictive factors	Demographic data, parents rating of child behaviour, teachers rating of child's behaviour, previous treatment, primary or secondary NE, UTI, day time wetting, soiling, family difficulties, housing	NE population
Jensen (1999) ⁷⁶	Questionnaire on child's wetting habits	Questions on how often the child wet before and after treatment, did the child become totally dry, child dry 1 year after treatment	Bed wetting
Schaumburg (2001) ¹³⁴	Family history	Family history of NE, including secondary NE and duration of NE	Treatment resistant children

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Houts (1984) ⁷²	Previous treatment with imipramine	pre - treatment variables: prior treatment with imipramine, age, gender, family history, length of treatment	Treatment resistant children
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Table 6-4: Prediction studies - Results

Author	Setting	Outcome	Prevalence	Impact on treatment
Radiological				
Persson (1993) ¹¹⁹	FRG	Urodynamic findings on success rates of oxybutynin	Not reported	Children with uninhibited bladder contractions, graduation of detrusor instability, reduced bladder capacity and the extent of volume decrease were all more successful in the treatment with oxybutynin
Investigations				
Evans (1992) ⁵³	UK	Factors associated with desmopressin success	Not reported	None of the parameters influenced success rates for treatment with desmopressin
Eller (1998) ⁴⁹	Canada and USA	Factors linked with successful treatment with desmopressin	Not reported	The study showed daytime functional bladder capacity, maximal functional bladder capacity expressed as a percentage of normal and age were significant predictors of response to desmopressin. The study showed children with 70% or more bladder capacity had an 83% chance of success with desmopressin.
History				

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Kruse (1999) ⁸⁵	Sweden	Dryness due to changing drinking and voiding habits	Not reported	After 1 month all children had significantly improved the number of dry nights
Devlin (1990) ⁴⁰	Local health clinics, Ireland	Factors for successful treatment with alarms	Not reported	Success at 6 months was associated with absent stressful events, absent psychiatric disorders, absent family stress, having family and parental concern and having the child rate distress as moderate to great. Factor associated with the outcome at 12 months were rarely day time wetting, absence of urological disorder, absence of psychiatric disorder, absence of developmental delay, having great or moderate parental concern and having moderate or great child distress
Butler (1990) ³¹	UK	Successful treatment with alarms	Not reported	Absence of resistance constructs and having perceived family support meant children were more likely to be successful treated with an alarm
Butler (1998) ²¹	Hospital, UK	Factors linked with successful treatment with desmopressin	Not reported	Wet for fewer nights before treatment, parental belief child's enuresis was unstable and a higher birth weight were all linked to the child being successfully treated with desmopressin
Kruse (2001) ⁸⁴	Sweden	Factors linked with successful treatment with desmopressin	Not reported	Being older and having fewer wet nights before treatment led to successful treatment with desmopressin

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Butler (1990) ²⁵	UK	Pre-treatment variables leading to relapse	Not reported	Children who relapsed after successful treatment with Alarms of modified DBT, were more likely to have over 16 wet nights during treatment period of 16 weeks, more likely to have previously tried an alarm, more likely to attribute their bedwetting to drinking too much before going to bed, less likely to attribute it to being too cold to arise from bed in the night, more likely to have secondary NE, more likely not to worry about bedwetting. the study says the last two are most significant with the power of the study
Fielding (1985) ⁵⁷	Specialist enuresis clinic for the study, UK	Response to retention control training and an alarm or an alarm alone	Not reported	Treatment failure after 14 weeks of treatment was linked to frequency of micturition, urgency or micturition, previous experience of alarm treatment. Relapse at 12 months was not linked to any of the pre treatment variables
Dische (1983) ⁴³	UK	Successful treatment with alarms	Not reported	Unsatisfactory housing, family difficulties adversely impacted on initial success with an alarm. Teacher ratings of behaviour and family difficulties impacted on relapse rates
Jensen (1999) ⁷⁶	Denmark	Relationship between wetting habits and success	Not reported	Children with more wet nights before treatment responded better to alarms as did

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		rates with alarms		girls and children over 10 years - unclear assumptions
Schaumburg (2001) ¹³⁴	Enuresis Clinic, Hospital, Denmark	% with family history and response to desmopressin	Statistically significantly more children with NE had a family history of NE compared to children without NE	There was no difference in the response to desmopressin between children with or without a family history of NE
Houts (1984) ⁷²	USA	Relapse after alarm treatment	Not reported	Relapse after an alarm treatment was more likely in children who had previously been treated with imipramine. Age, gender, family history and length of treatment did not predict relapse

Table 6-5: Evidence statements

Tanaka (2003)¹⁴⁶

- One observational study showed having a positive history of NE in siblings and frequency were both statistically more common in children with reflux.

Nappo (2002)¹⁰⁹

- One observational study showed 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).

Schaumburg (2001)¹³⁴

- One observational study showed 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.

Cayan (2001)³⁴

- One observational study showed a statistically significant difference in the number of children with constipation between the children with NE and control children.

McGrath (2008)¹⁰¹

- One observational 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.

O'Regan (1986)¹¹⁶

- One observational study strongly implicated unrecognized rectal distention as an etiologic factor of enuresis and treatment for constipation lead to children becoming initially dry.

Robson (2005)¹³⁰

- One observational study showed the only significant difference between children with PNE and SNE was constipation with more children with SNE having constipation.

Siegel (1976)¹³⁸

- One observational study showed there was no statistical difference between the number of children with persistent NE (night wetting every week) between children previously 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) between children with allergies and controls (13% in allergy group and 23% in control group).

Butler (2004)³²

- One observational study showed there were no predictive factors for desmopressin response, 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.

- One observational study showed the following were significant in predicting outcome of desmopressin treatment: 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.
- One observational study showed children who relapsed after alarms or modified dry bed training 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.
- One observational study showed the probability of successful treatment with an alarm increases with age but decreases with the presence of resistance constructs

Evans (1992) ⁵³

- One observational 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 not significantly change the response rate.

Kruse (2001) ⁸⁴

- One observational study showed there was a significant difference in the response rate to desmopressin for 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, the frequency of wetting was also significantly different with more frequent being less likely to respond.

Devlin (1990) ⁴⁰

- One observational 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 after alarm treatment. 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 after alarm treatment.

Fielding (1985) ⁵⁷

- One observational study showed three variables were associated with alarm treatment failure: frequency of micturition, urgency of micturition and previous experience of alarm treatment. None of the 30 variables were associated with relapse after alarm treatment.

Dische (1983) ⁴³

- One observational study showed unsatisfactory housing and family difficulties adversely affect initial success with alarm treatment. The study showed children with deviant scores on the teacher's rating scale and the presence of family difficulties were related to relapse with alarm treatment. The study showed deviant scores on the teacher's rating scale and the presence of family difficulties adversely affects long-term success with alarm treatment.

Jensen (1999) ⁷⁶

- One observational study showed patients with the highest number of wet nights were more successful with alarm treatment than those with fewer wet nights. The study showed age and gender impact on treatment response.

Houts (1984) ⁷²

- One observational study showed prior treatment with imipramine was significantly associated with relapse after alarm treatment.

6.4.2 Evidence to recommendations

Relative values of different outcomes

The aim of assessment is to make a diagnosis of bedwetting with or without daytime symptoms, to exclude other conditions that may present as bedwetting and to develop a management plan appropriate to the child and family.

Trade off between clinical benefit and harms

No harms were identified in the evidence

Economic considerations

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No economic evidence was identified to inform recommendations on clinical assessment, but the GDG felt that an assessment asking the recommended questions would allow clinicians to tailor treatment to the individual child's needs and ultimately help the child to achieve the desired outcome. The GDG felt that routine urinalysis was not clinically useful and therefore represented an unnecessary cost. The GDG also felt that identification of comorbidities or other factors could influence both choice and outcome of treatment which could impact the relative cost-effectiveness of interventions.

Quality of evidence (this includes clinical and economic)

The evidence that was available came from cohorts or case series and were generally of highly selective populations often in secondary or tertiary referral centres. The cohorts were often small and there was a lack of conclusive evidence. The GDG were interested in possible associations between symptoms and underlying problems, factors that predicted response to treatment and for relapse prevention to inform their recommendations. A significant association or predictor of response might indicate a subgroup who would require a different strategy if the evidence on interventions was supportive of this. The GDG reviewed the evidence but given the poor quality of evidence the discussion and recommendations were primarily informed by the professional opinion of the GDG from clinical knowledge, understanding of pathophysiology of bedwetting and the patient and carer member's personal experiences.

Other considerations

While the majority of children presenting with bedwetting will not have an underlying systemic illness, the GDG considered it important that healthcare professionals should consider such conditions as diabetes and urinary tract infection if the history is recent.

Although the treatment of secondary onset bedwetting is similar to that of primary onset bedwetting, the GDG considered it important to assess if there were any specific triggers to the onset of secondary bedwetting. These might require assessment and management instead of or alongside the management of bedwetting.

The GDG considered whether all children presenting with bedwetting required routine urinalysis. The GDG considered that an absolute requirement for urinalysis was suspicion of diabetes, urinary tract infection, signs of ill health, recent onset of bedwetting or when child had daytime symptoms. There was no epidemiological or cohort evidence examining prevalence of abnormal urinalysis in populations with bedwetting. The professional experience of the GDG was that untargeted urinalysis

was not necessarily clinically worthwhile and did have a financial cost. The GDG considered that a recommendation saying 'do not perform urinalysis routinely' gave clinicians permission to use clinical judgement but indicated that routine urinalysis was not a requirement in assessment of children.

Bedwetting does frequently exist in combination with daytime urinary symptoms, constipation, and disorders such as ADHD and the presence of these symptoms or conditions may also be a factor in deciding on appropriate treatment. Children whose daytime symptoms are severe might in the experience of the GDG do best by treating the daytime symptoms first. The assessment and treatment of daytime wetting is outside the scope of the guideline but the GDG considered that there is such overlap between these symptoms that health care professionals needed at a minimum to be alerted to whether a child or young person has significant day time symptoms. The GDG considered that children with severe day time symptoms might warrant treatment of these symptoms before considering treatment of bedwetting specifically.

The GDG considered that asking families whether they had restricted fluid intake is important as families may try this in the belief that it will help their child remain dry at night.

The GDG considered that an important part of the clinical assessment was an assessment of the interest of the child in treatment, and whether the child and family would be able to take part in behavioural interventions such as alarm treatment. This treatment might be an added burden for some children and parents particularly if parents report feeling angry towards child. These parents may need additional support. The evidence review on the impact of bedwetting on child and family also informed the recommendations on assessment.

The GDG considered it important that healthcare professionals know how to interpret the responses to the questions recommended during assessment. The GDG developed a table to outline the important aspects of history; this was generated using accepted classification of bedwetting and daytime symptoms and using consensus among the GDG. Attempting to provide this information using individual recommendations resulted in recommendations that were excessively complex and difficult to follow. This table can be found in section 1.3.18.

6.4.3 Recommendations

6.4.3.1 Ask whether the bedwetting started in the last few days or weeks. If so, consider whether this is a presentation of a systemic illness.[1.3.1]

- 6.4.3.2 *Ask if the child had previously been dry at night without assistance for 6 months. If so, enquire about any possible medical, emotional or physical triggers, and consider whether assessment and treatment is needed for any identified triggers. [1.3.2]*

- 6.4.3.3 *Ask about the pattern of bedwetting, including questions such as:*
- *How many nights a week does bedwetting occur?*
 - *How many times a night does bedwetting occur?*
 - *Does there seem to be a large amount of urine?*
 - *At what times of night does the bedwetting occur?*
- Does the child wake up after bedwetting? [1.3.3]*
- 6.4.3.4 *Ask about the presence of any daytime symptoms in a child with bedwetting, including:*
- *daytime frequency (that is, passing urine more than seven times a day)*
 - *daytime urgency*
 - *daytime wetting*
 - *passing urine infrequently (fewer than four times a day)*
 - *abdominal straining or poor urinary stream*
 - *pain passing urine. [1.3.4]*
- 6.4.3.5 *Ask about daytime toileting patterns in a child with bedwetting, including:*
- *whether daytime symptoms occur only in some situations*
 - *avoidance of toilets at school or other settings*
 - *whether the child goes to the toilet more or less frequently than his or her peers.[1.3.5]*
- 6.4.3.6 *Ask about the child's fluid intake throughout the day. In particular, ask whether the child or the parents or carers are restricting fluids.[1.3.6]*
- 6.4.3.7 *Do not perform urinalysis routinely in children with bedwetting, unless any of the following apply:*
- *bedwetting started in the last few days or weeks*
 - *the child has daytime symptoms*
 - *the child has any signs of ill health*
 - *there is a history, symptoms or signs suggestive of urinary tract infections*
 - *there is a history, symptoms or signs suggestive of diabetes mellitus.[1.3.8]*

- 6.4.3.8 *Assess whether the child has any comorbidities or there are other factors to consider, in particular:*
- constipation and/or soiling
 - developmental, attention or learning difficulties
 - diabetes mellitus
 - behavioural or emotional problems
 - family problems or vulnerable child or family.[1.3.9]
- 6.4.3.9 *Consider assessment, investigation and/or referral when bedwetting is associated with:*
- severe daytime symptoms
 - a history of recurrent urinary infections
 - known or suspected physical or neurological problems
 - comorbidities or other factors (as for example, those listed in recommendation 1.3.9).[1.3.10]
- 6.4.3.10 *Investigate and treat children with suspected urinary tract infection in line with 'Urinary tract infection' (NICE clinical guideline 54).[1.3.11]*
- 6.4.3.11 *Investigate and treat children soiling or constipation in line with 'Constipation in children and young people' (NICE clinical guideline 99).[1.3.12]*
- 6.4.3.12 *Children and young people with suspected type 1 diabetes should be offered immediate (same day) referral to a multidisciplinary paediatric diabetes care team that has the competencies needed to confirm diagnosis and to provide immediate care [This recommendation is from 'Type 1 diabetes' (NICE clinical guideline 15). [1.3.13]*
- 6.4.3.13 *Consider investigating and treating daytime symptoms before bedwetting if daytime symptoms predominate.[1.3.14]*
- 6.4.3.14 *Consider involving a professional with psychological expertise for children with bedwetting and emotional or behavioural problems. [1.3.15]*
- 6.4.3.15 *Discuss factors that might affect treatment and support needs, such as:*
- the child's sleeping arrangements (for example, does the child have his or her own bed or bedroom)
 - the impact of bedwetting on the child and family

- *whether the child and parents or carers have the necessary level of commitment, including time available, to engage in a treatment programme.[1.3.16]*

6.4.3.16 Use the findings of the history to inform diagnosis (according to table 1) and management of bedwetting.

Table 1 Findings from the history and their possible interpretation

Findings from history	Possible interpretation
Large volume of urine in the first few hours of night	Typical pattern for bedwetting only.
Variable volume of urine, often more than once a night	Typical pattern for children who have bedwetting and daytime symptoms with possible underlying overactive bladder.
Bedwetting every night	Severe bedwetting is less likely to resolve spontaneously than infrequent bedwetting.
Previously dry for more than 6 months	Bedwetting is defined as secondary.
<ul style="list-style-type: none"> •Daytime frequency •Daytime urgency •Daytime wetting •Abdominal straining or poor urinary stream •Pain passing urine 	Any of these may indicate the presence of a bladder disorder such as overactive bladder or more rarely (when symptoms are very severe and persistent) an underlying urological disease.
Constipation	A common comorbidity that can cause enuresis and required treatment (see 'Constipation in children' [NICE clinical guideline 99]).
Soiling	Frequent soiling is usually secondary to underlying faecal impaction and constipation which may have been unrecognised.
Inadequate fluid intake	May mask an underlying bladder problem such as overactive bladder disorder and may impede the development of an adequate bladder capacity.
Behavioural and emotional problems	These may be a cause or a consequence of bedwetting. Treatment may need to be tailored to the specific requirements to each child and family.
Family problems	A difficult or 'stressful' environment may be a trigger for bedwetting. These factors should be addressed alongside the management of bedwetting.

Practical issues	Easy access to a toilet at night, sharing a bedroom or bed and proximity of parents to provide support are all important issues to consider and address when considering treatment, especially with an alarm.
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[1.3.19]

6.5 *What is the incremental benefit and cost effectiveness of radiological examination, in the evaluation of children and young people under 19 years old who have bedwetting?*

6.5.1 Evidence review

See tables at 6.4.1.1 for outline of studies included.

6.5.2 Evidence statements

Van Der Vis-melsen (1992)¹⁵³

- One observational study showed aimed to identify abnormalities probably related to NE, see extraction for details. There were no comparisons made in the study

Yeung (2004)¹⁷¹

- One observational 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

Redman (1979)¹²⁵

- One observational study showed 21 children had a significant abnormality noted wither on IVP or cystography. 2 children produced any yield of significant abnormal findings; UTI documented by history or confirmed by urinalysis and / or culture and symptoms and signs of lower urinary tract obstruction. The authors reported a history of diurnal enuresis did not indicate significant findings unless the patients also had an infection or obstruction.

Cutler (1978)³⁷

- One observational study showed 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.

Sujka (1991) ¹⁴³

- One observational 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.

Zink (2008) ¹⁷³

- One observational 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

Van Hoacke (2007) ¹⁵⁴

- One observational study aimed to identify abnormalities but did not give a comparison. See extraction for details.

Persson-Junemann (1993) ¹¹⁹

- One observational study showed children with uninhibited bladder contractions, graduation of detrusor instability, reduced bladder capacity and the extent of volume decrease were all more successful in the treatment with oxybutynin

Kruse (1999) ⁸⁵

- One observational study showed after 1 month all children treated for micturition were significantly drier

Eller (1998) ⁴⁹

- One observational study showed daytime functional bladder capacity, maximal functional bladder capacity expressed as a percentage of normal and age were significant predictors of response to desmopressin

Riccabona (1998) ¹²⁸

- One observational study showed 71% of children achieved complete dryness with no relapses and remained dry without treatment with the withdrawal program from desmopressin.

Butler (2001)³⁰

- One observational study showed at weeks 9 and 10 and at 6 months success was associated with a higher number of dry medication nights and no medication nights after a structured withdrawal from desmopressin or imipramine.

6.5.3 Evidence to recommendations

Relative values of different outcomes

The aim of investigations would be to exclude other conditions that may present with bedwetting as symptoms and to guide a management plan appropriate to the child and family.

Trade off between clinical benefit and harms

The GDG did not consider there was clinical benefit for the majority of children in performing radiological investigations and there might be significant harm in terms of discomfort and radiation exposure.

Economic considerations

No economic evidence was identified to inform the cost-effectiveness of radiological investigation in all children with bedwetting, however the GDG felt it was extremely unlikely to be cost-effective.

Quality of evidence (this includes clinical and economic)

The GDG considered that the majority of children with bedwetting did not require investigation of bladder anatomy or function using invasive testing. An adequate history should pick up those children who may require specialist assessment. The evidence came from highly selected populations and was not generalisable to the general population with bedwetting. The GDG agreed that bladder anatomy and child's ability to empty bladder may need to be investigated when children who do not respond to treatment are assessed but that this decision needs to be made on an individual basis by experienced healthcare professionals.

6.6 *What are the core elements of bladder diaries and other assessment tools, in the evaluation of children and young people under 19 years old who have bedwetting?*

6.6.1 Evidence review

See table in 6.4.1.1 above for information on studies.

6.6.2 Evidence statements

Kwak (2008) ⁸⁶

- One observational study showed there were differences in the results of a non validated LUTS questionnaire and the bladder diaries.

6.6.3 Evidence to recommendations

Relative values of different outcomes

The aim of assessment is to make a diagnosis of bedwetting with or without daytime symptoms, to exclude other conditions that may present with bedwetting as symptoms and to develop a management plan appropriate to the child and family.

Trade off between clinical benefit and harms

The GDG considered that the use of charts was a useful way for the child and family to focus on the problem and would be unlikely to be harmful.

Economic considerations

No economic evidence was identified. The GDG considered that the use of bladder charts and diaries requires at least a 2-phase assessment, an initial visit during which patients are asked to record symptoms and activity and a follow-up to use the record in determining treatment. The lack of clinical data to support bladder charts and diaries and the considerable resource use implications of their implementation led the GDG to recommend their use in a subset of patients they consider may benefit.

Quality of evidence (this includes clinical and economic)

There was no evidence available evaluating the usefulness of chart/diaries. The GDG had considerable experience in using bladder charts and diaries in clinical practice.

Other considerations

The GDG considered that understanding the symptoms experienced by a child, and the child's drinking and toileting behaviour is extremely important in making a good assessment and management plan. Parents or carers are often not aware of their child's drinking and toileting behaviour once children spend a lot of their time outside the home. The recording of these can help the child and family recognize the problem and often monitor progress. When children are managed in pull ups or nappies it can sometimes be useful to weigh these to inform an understanding of how much urine children are passing at night compared to how much they pass when urinating during the day. The GDG considered that as with charting, one of the main benefits of this is the understanding of the problem by child and family.

The GDG discussed whether all children and families should be required to do charting and considered that they could not recommend this as this was potentially onerous for some families and because of the lack of evidence for the use of this strategy on a routine basis.

The GDG discussed whether it was possible to specify how long such recording should take place for. The consensus was that for day time wetting 2 days would usually be adequate to understand the pattern of wetting and 2 weeks would be required to establish the pattern of bedwetting. The GDG considered that healthcare professionals would need to make individual judgement as to what to recommend for each family according to symptoms and family situation.

6.6.4 Recommendations

6.6.4.1 *Consider whether a record of the child's fluid intake, daytime symptoms, bedwetting and toileting patterns would be useful in the assessment and management of bedwetting. If so, consider asking the child and parents or carers to record this information.[1.3.7]*

6.7 How should a psychological assessment be conducted, in the evaluation of children and young people under 19 years old who have bedwetting?

6.7.1 Evidence statements

Van Hoecke (2004)¹⁵⁵

- One observational study showed 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, social desirability.

6.7.2 Evidence review

See table 6.4.1.1 for information on studies

6.7.3 Evidence to recommendations

Relative values of different outcomes

The aim of a psychological assessment is to exclude other conditions that may present with bedwetting as symptoms, consider whether there are significant psychological issues that need addressing in their own right instead of or alongside the management of bedwetting and to develop a management plan appropriate to the child and family.

Trade off between clinical benefit and harms

No evidence was found,

Economic considerations

No economic evidence was identified, but routine psychological assessment for children with bedwetting would represent a substantial cost to the NHS, one not supported by the clinical evidence.

Quality of evidence (this includes clinical and economic)

There was no evidence

Other considerations

The GDG considered that there was not enough evidence to suggest that all children with bedwetting required psychological assessment. Healthcare professionals need to be alert to those children whose bedwetting is part of emotional, behavioural or family problems and should consider whether these children require referral to specialists. The GDG noted the evidence regarding the impact of bedwetting which indicates that bedwetting itself results in loss of self esteem and that engagement in treatment helps self esteem.

6.8 What is the 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?

6.8.1 Evidence statements

Support and follow up

No studies

No evidence was identified which considered the clinical effectiveness of additional investigation and treatment in children who have not responded to an adequate trial of desmopressin and/or alarms.

6.8.2 Evidence to recommendations

Relative values of different outcomes

The aim of investigations would be to exclude other conditions that may present with bedwetting as symptoms, and may explain lack of response to initial treatments and to develop a management plan appropriate to the child and family.

Trade off between clinical benefit and harms

The GDG considered that it would be inappropriate to recommend routine testing of children when they do not respond to treatment without evidence of significant benefit in yield of abnormal diagnoses or improved response to treatment.

Economic considerations

No economic evidence was identified, but as there are many children who will not respond to desmopressin and/or alarms, investigating their symptoms further is very unlikely to be cost-effective.

Quality of evidence (this includes clinical and economic)

The GDG considered that the majority of children with bedwetting did not require investigation of bladder anatomy. There was no evidence of what investigations might be required for children not responding to treatment and the GDG considered from their clinical experience that most would not need investigation and that this required individual assessment. The GDG did report that ultrasonography is increasingly used in secondary care and that with improved and easier access to newer generation machines this area is likely to need proper evaluation.

7 Fluid and diet restriction for the management of bedwetting

7.1 Introduction

The experience of health professionals is that parents or carers may consider the restriction of fluids a possible management strategy when trying to help a child with bedwetting. Restriction of fluids particularly before bed will have been tried by many families before they seek professional help. Children with bedwetting may also have daytime urinary symptoms and fluid restriction during the day may be used by children and young people themselves to manage symptoms of frequency and urgency when out of the home. Optimum hydration is essential for general health of children and children who are restricting fluids during the day may in fact take excessive fluid before bedtime to balance their relative dehydration during the day. The presence or absence of toilet facilities and drinks in schools, and the condition of facilities available may also affect toileting behaviour and drinking habits

The hypothesis that dietary restrictions may be beneficial to children with bedwetting is based on the idea that food allergies may provoke bladder instability.

7.2 *What is the clinical and cost effectiveness of fluid and/or diet restriction for children and young people under 19 years who have bedwetting?*

7.3 Fluid restriction

7.3.1 Evidence review

7.3.1.1 *Fluid restriction combined with parents avoiding punishment of children and waking and placebo compared to imipramine*

One randomised controlled trial **Bhatia (1990)**¹² compared fluid restriction combined with parents avoiding punishment of children and waking and placebo to imipramine. The study population were children who had bedwetting and possible daytime wetting. 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.

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Table7-1: Fluid restriction and avoiding punishment with placebo compared to imipramine - Clinical summary of findings

Outcome	Fluid restriction	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	4/20 (20%)	12/20 (60%)	RR 0.33 (0.13 to 0.86)	402 fewer per 1000 (from 84 fewer to 522 fewer)	VERY LOW

7.3.1.2 *Fluid restriction combined with parents avoiding punishment of children and waking and placebo compared to fluid restriction combined with parents avoiding punishment of children and waking and imipramine*

One randomised controlled trial **Bhatia (1990)**¹² compared fluid restriction combined with parents avoiding punishment of children and waking and placebo to fluid restriction combined with parents avoiding punishment of children and waking and imipramine. The study population and methods are as described above.

Table 7-2: Fluid restriction and avoiding punishment with placebo compared to fluid restriction and avoiding punishment with imipramine - Clinical summary of findings

Outcome	Fluid restriction	Fluid restriction and imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	4/20 (20%)	18/20 (90%)	RR 0.22 (0.09 to 0.54)	702 fewer per 1000 (from 414 fewer to 819 fewer)	VERY LOW

7.3.2 Evidence statements

Studies which include children with bedwetting and possible daytime symptoms

Bhatia (1990)¹²

- One study showed that children treated with imipramine were more likely to achieve 14 consecutive dry nights compared to children treated with fluid restriction combined with avoiding punishment and waking and placebo. Relative risk 0.33 95% CI 0.13, 0.86. Children had an age range of 4 to 12 years and treatment was for 6 weeks.

- One study showed that children treated with fluid restriction combined with avoiding punishment and waking and imipramine were more likely to achieve 14 consecutive dry nights compared to children treated with fluid restriction combined with avoiding punishment and waking and placebo. Relative risk 0.22 95% CI 0.09, 0.54. Children had an age range of 4 to 12 years and treatment was for 6 weeks.

7.3.3 Evidence to recommendations

Relative values of different outcomes

The GDG considered that complete dryness was the outcome most wanted by children and their families.

Trade off between clinical benefit and harms

The GDG felt that restriction of fluids was likely to be unhealthy for children generally and may be counterproductive in helping children recognise the sensation of full bladder and developing control.

Economic considerations

No economic evidence regarding the cost-effectiveness of fluid and/or dietary restriction was available, however the GDG felt that encouraging adequate fluid intake (and thus discouraging fluid restriction) should be one element of advice offered to all patients seeking initial treatment for bedwetting. Adequate fluid intake during the day may naturally reduce a child's intake just before bed and could therefore reduce their burden of bedwetting without requiring further, costlier treatment.

Quality of evidence (this includes clinical and economic)

No evidence for fluid restriction was found. One RCT which compared fluid restriction, waking and lack of punitive approach in evenings with imipramine was found. This evidence was considered very low quality.

Other considerations

The evidence found no benefit from restricting fluid intake. The consensus of the GDG was that it is important to actively raise the issue of fluid intake with children and families to counter any misconceptions about fluid restriction. The presence or absence of daytime symptoms may also not be apparent if children or families are restricting fluids. Ensuring adequate intake during the day also may prevent children from needing to drink larger amounts nearer bedtime.

The GDG considered it important to provide children and families with a guide to desirable fluid intake. There is no single recommended figure for fluid intake in

children as fluid requirements are influenced by numerous factors including size, dietary intake, activity levels and ambient temperature. The human body can regulate its water content over a wide range of fluid intakes and prevent both dehydration and over hydration. Water intake comes from both drinks and food intake and both these values can vary enormously between individuals.

The GDG considered the information provided by government bodies and experts and the most comprehensive source of information on water requirements is:

Dietary reference intakes for water, potassium, sodium, chloride, and sulphate. Panel on Dietary Reference Intakes for Electrolytes and Water Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board. Institute of Medicine (U.S). 2004.¹¹⁸

The reference values provided in this document describe “Adequate Intake” as the median intake of total water in different age bands documented in the U.S Third National Health & Nutrition Survey 1988-1994. These values were chosen because of data demonstrating that hydration was maintained over a wide range of fluid intakes varying from the 10 percentile to the 90th percentile of fluid intake. The document is very clear that it is not possible to provide a recommended fluid intake.

In applying these figures to children with bedwetting in the UK, the GDG considered that the extremes of fluid intake were undesirable in that insufficient fluid intake may inhibit the development of normal toileting patterns and mask the symptoms of bladder disorders whilst excessive fluid intake, especially before bed time may provoke wetting. We have therefore given guidance on the ranges of total intake from drinks (this is easier to measure and hence influence than including fluid associated with non-drinks intake) and have taken this as the inter-quartile range of fluid intakes (rounded to nearest 100 ml). This then provides a guideline minimum and maximum fluid intake although these figures need to be considered in relation to each individual’s circumstances and health status and adapted accordingly.

The GDG noted there was no evidence about the effect of fizzy drinks. The GDG were concerned that many children might be drinking caffeine containing drinks (which are diuretic) and that these might not be helpful in general or specifically for urinary symptoms and felt this was a good opportunity to reiterate these messages.

The GDG wished to give children and families some indication of normal toileting frequency and consensus was to use the standardized International Children’s Continence Society (ICCS) criteria. The ICCS suggest <3 times per day is abnormal and >8 times per day is abnormal. These figures were judged by the GDG to be extremes indicated abnormality and a midway figure of 4-7 was more reasonable range when recommending to parents and carers.

It was the experience of the GDG that children, including children with behavioural or attention difficulties, may be managed by parents and carers in pull ups/nappies and that a trial without this should be considered if they are toilet trained by day.

7.3.4 Recommendations

7.3.4.1 Advise children with bedwetting and their parents or carers that:

- *adequate daily fluid intake is important in the management of bedwetting.*
- *daily fluid intake varies according to ambient temperature, dietary intake and physical activity. A suggested intake of drinks is given in table 2:*

Table 2 Suggested daily intake of drinks for children and young people

Age	Sex	Total drinks per day
4–8 years	Female	1000–1400 ml
	Male	1000–1400 ml
9–13 years	Female	1200–2100 ml
	Male	1400–2300 ml
14–18 years	Female	1400–2500 ml
	Male	2100–3200 ml

[1.5.1]

7.3.4.2 Advise the child and parents or carers that the consumption of caffeine-based drinks should be avoided in children with bedwetting. [1.5.2]

7.3.4.3 Advise the child of the importance of using the toilet at regular intervals throughout the day.[1.5.4]

7.3.4.4 Advise parents or carers to encourage the child to use the toilet to pass urine at regular intervals during the day (typically between four and seven times in total). This should be continued alongside the chosen treatment for bedwetting.[1.5.5]

7.3.4.5 Address excessive or insufficient fluid intake or abnormal toileting patterns before starting other treatment for bedwetting in children.[1.5.6]

7.3.4.6 Suggest a trial without nappies or pull-ups for a child with bedwetting who is toilet trained by day and is wearing nappies or pull-ups at night.[1.5.7]

7.4 Dietary restriction

7.4.1.1 Diet restriction compared to imipramine

One randomised controlled trial, **McKendry (1975)**¹⁰² compared diet restriction to imipramine. Diet restriction was described as a diet containing no milk, butter, cheese, eggs, citrus fruit juices, tomato, cocoa or chocolate. Children were allowed apple juice, ginger ale and water as fluid substitutes. The study population was children who had bedwetting and possible daytime wetting.

Table 7-3: Diet restriction compared to Imipramine - Clinical summary of findings

Outcome	Diet restriction	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who became completely dry	1/64 (1.6%)	13/62 (21%)	RR 0.07 (0.01 to 0.55)	195 fewer per 1,000	LOW
Number of children who had a greater than 50% improvement in the number of dry nights	34/64 (53.1%)	28/62 (45.2%)	RR 1.18 (0.82 to 1.68)	81 more per 1,000	VERY LOW
Number of children completely dry at follow up	1/1 (100%)	19/34 (55.9%)	RR 1.35 (0.57 to 3.16)	195 more per 1,000	VERY LOW
Number of children who had a greater than 50% improvement in the number of dry nights at follow up	0/1 (0%)	8/34 (23.5%)	RR 1.03 (0.09 to 12.18)	7 more per 1,000	VERY LOW
Number of children who dropped out of the trial	9/73 (12.3%)	12/74 (16.2%)	RR 0.76 (0.34 to 1.69)	38 fewer per 1,000	VERY LOW

7.4.2 Evidence statements

Studies included children with bedwetting and possible daytime symptoms

McKendry (1975) ¹⁰²

- One study showed that children treated with imipramine were more likely to become completely dry at the end of treatment compared to children treated with diet restriction. Relative risk 0.07, 95% CI 0.01, 0.55. Children had a mean age of 9 years and treatment was for 2 months.
- One study showed there was no statistically significant difference in the number of children who achieved greater than 50% improvement in the number of dry nights at the end of treatment between children treated with diet restriction and children treated with imipramine. Relative risk 1.18, 95% CI 0.82, 1.68. Children had a mean age of 9 years and treatment was for 2 months.
- One study showed there was no statistically significant difference in the number of children who were completely dry at follow up between children treated with diet restriction and children treated with imipramine. Relative risk 1.35, 95% CI 0.57, 3.16. Children had a mean age of 9 years and treatment was for 2 months.
- One study showed there was no statistically significant difference in the number of children who achieved greater than 50% improvement in the number of dry nights at follow up between children treated with diet restriction and children treated with imipramine. Relative risk 1.03, 95% CI 0.09, 12.18. Children had a mean age of 9 years and treatment was for 2 months.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with diet restriction and children treated with imipramine. Relative risk 0.76, 95% CI 0.34, 1.69. Children had a mean age of 9 years and treatment was for 2 months.

7.4.3 Evidence to recommendations

Relative values of different outcomes

The GDG considered the outcome of complete dryness was the outcome wanted by children and families.

Trade off between clinical benefit and harms

No evidence of harms.

Economic considerations

No economic evidence was identified.

Quality of evidence (this includes clinical and economic)

The quality of evidence for outcomes was low or very low..

Other considerations

The GDG wished to explore this area as they were aware of families who asked about associations between dietary intolerance and bedwetting. No evidence was found that routinely restricting diet is effective in improving bedwetting in the short or long term. The GDG felt it was important to ensure the child was eating healthily.

7.4.4 Recommendations

- 7.4.4.1 Advise the child and parents or carers to eat a healthy diet and not to restrict diet as a form of treatment for bedwetting in children. [1.5.3]*

8 Lifting and waking in the management of bedwetting

8.1 Introduction

Lifting is described as lifting the child from their bed while they sleep or walking the child to the bathroom to pass urine, without necessarily waking the child. Waking is described as waking the child from their sleep and taking them to the bathroom to pass urine. Children can be woken at either set times or randomly during the night. Traditionally these methods have been used by families to manage bedwetting and the GDG were interested in their use and any potential benefits or harms so that families could be appropriately advised.

The evidence review on the effectiveness of waking assessed waking compared to no treatment; waking compared to other treatments; waking compared to combination of treatments. No evidence on lifting was found.

8.2 What is the clinical and cost effectiveness of lifting and waking for children and young people under 19 years who have bedwetting?

8.2.1 Evidence review

Evidence review

8.2.1.1 Random waking compared to placebo

Two randomised controlled trials, **Fournier (1987)**⁶⁰ and **Turner (1970)**¹⁵⁰ compared random waking to placebo. **Fournier (1987)**⁶⁰ described random waking as the parent waking the child any time before midnight; **Turner (1970)**¹⁵⁰ described random waking as the parents being given a chart with random times on it at when the child should be woken.

Table 8 -1: Random waking compared to placebo - Clinical summary of findings

Outcome	Random waking	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	1/15 (6.7%)	4/17 (23.5%)	RR 0.28 (0.04 to 2.26)	169 fewer per 1000 (from 226 fewer to 296 more)	VERY LOW

Mean wet nights per week at 4 weeks	15	17	-	MD -0.99 (-2.54 to 0.56)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	8	8	-	not pooled	VERY LOW

8.2.1.2 Random waking compared to imipramine

One randomised controlled trial, **Fournier (1987)**⁶⁰ compared random waking to imipramine. Random waking was described as the parent waking the child any time before midnight.

Table 8-2: Random waking compared to imipramine - Clinical summary of findings

Outcome	Random waking	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights	8	8	-	not pooled	VERY LOW

8.2.1.3 Random waking compared to enuresis alarm

Two randomised controlled trials, **Fournier (1987)**⁶⁰ and **Turner (1970)**¹⁵⁰ compared random waking to enuresis alarm. **Fournier (1987)**⁶⁰ described random waking as the parent waking the child any time before midnight; **Turner (1970)**¹⁵⁰ described random waking as the parents being given a chart with random times on it at when the child should be woken.

Table 8-3: Random waking compared to enuresis alarm - Clinical summary of findings

Outcome	Random waking	Enuresis alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	1/15 (6.7%)	3/15 (20%)	RR 0.33 (0.04 to 2.85)	134 fewer per 1000 (from 192 fewer to 370 more)	VERY LOW
Mean wet nights per week at 4 weeks	15	15	-	MD 0.33 (-1.23 to 1.89)	VERY LOW

Mean number of wet nights per week at the end of treatment (no sd)	8	8	-	not pooled	VERY LOW
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8.2.1.4 Random waking compared to enuresis alarm and imipramine

One randomised controlled trial, **Fournier (1987)**⁶⁰ compared random waking to an enuresis alarm and imipramine. Random waking was described as the parent waking the child any time before midnight.

Table 8-4: Random waking compared to an enuresis alarm and imipramine - Clinical summary of findings

Outcome	Random waking	Alarm and imipramine	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights	8	8	-	not pooled	VERY LOW

8.2.1.5 Waking and star chart compared to no treatment

One randomised controlled trial, **Baker (1969)**⁷ compared waking and a star chart to no treatment, waiting list. 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 the start of the 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 to wake them for the two following nights.

Table 8 -5: Random waking and star chart compared to no treatment - Clinical summary of findings

Outcome	Random waking and star chart	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	2/14 (14.3%)	0/14 (0%)	RR 5 (0.26 to 95.61)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Mean number of wet nights	10	10	-	not pooled	VERY LOW

8.2.1.6 *Waking and star chart compared to enuresis alarm*

One randomised controlled trial, **Baker (1969)**⁷ compared waking and a star chart to an enuresis alarm. 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.

Table 8-6: Waking and star chart compared to enuresis alarm - Clinical summary of findings

Outcome	Waking and star chart	Alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	2/14 (14.3%)	11/14 (78.6%)	RR 0.18 (0.05 to 0.68)	645 fewer per 1000 (from 252 fewer to 747 more)	VERY LOW
Mean wet nights per week at 4 weeks	10	10	-	Not pooled	VERY LOW

8.2.1.7 *Waking (part of a 3 step program) compared to imipramine*

One randomised controlled trial, **Iester (1991)**⁷⁴ was identified. Children in the waking group took part in a three step program which was 1) reassurance to the parents and trying to encourage the child; 2) bladder retention training (drink more during the morning and afternoon, reduce the number of times voiding 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.

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Table 8-7: Waking (part of a 3 step program) compared to imipramine - Clinical summary of findings

Outcome	Waking	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	24/36 (66.7%)	14/36 (38.9%)	RR 1.71 (1.07 to 2.74)	276 more per 1000 (from 27 more to 677 more)	VERY LOW
Number of children who relapsed after 12 months	2/24 (8.3%)	2/14 (14.3%)	RR 0.58 (0.09 to 3.69)	60 fewer per 1000 (from 130 fewer to 385 more)	VERY LOW

8.2.1.8 *Waking (part of a 3 step program) compared to motivational therapy and 3 step program*

One randomised controlled trial, **Iester (1991)**⁷⁴ compared waking (part of a 3 step program) to motivational therapy and a 3 step program. Children in the waking 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. 3 step

Table 8-8: Waking (part of a 3 step program) compared to motivational therapy and 3 step program - Clinical summary of findings

Outcome	Waking	Motivational therapy	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	24/36 (66.7%)	81/96 (84.4%)	RR 0.79 (0.62 to 1.01)	177 fewer per 1000 (from 321 fewer to 8 more)	VERY LOW
Number of children who relapsed after 12 months	2/24 (8.3%)	3/81 (3.7%)	RR 2.25 (0.4 to 12.69)	46 more per 1000 (from 22 fewer to 433 more)	VERY LOW

8.2.1.9 *Waking combined with fluid restriction and parents avoiding punishment of children and placebo compared to imipramine*

One randomised controlled trial, **Bhatia (1990)**¹² compared waking combined with fluid restriction and parents avoiding punishment of children and placebo to imipramine. 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.

Table 8-9: Waking combined with fluid restriction and parents avoiding punishment of children and placebo compared to imipramine - Clinical summary of findings

Outcome	Waking and fluid restriction	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	4/20 (20%)	12/20 (60%)	RR 0.33 (0.13 to 0.86)	402 fewer per 1000 (from 84 fewer to 522 fewer)	VERY LOW
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8.2.1.10 Waking combined with fluid restriction and parents avoiding punishment of children and placebo compared to Waking combined with fluid restriction and parents avoiding punishment of children and imipramine

One randomised controlled trial **Bhatia (1990)**¹² compared waking combined with fluid restriction and parents avoiding punishment of children and placebo to waking combined with fluid restriction and parents avoiding punishment of children and imipramine. 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.

Table 8-10: Waking combined with fluid restriction and parents avoiding punishment of children and placebo compared to Waking combined with fluid restriction and parents avoiding punishment of children and imipramine - Clinical summary of findings

Outcome	Waking and fluid restriction	Waking and imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	4/20 (20%)	18/20 (90%)	RR 0.22 (0.09 to 0.54)	702 fewer per 1000 (from 414 fewer to 819 fewer)	VERY LOW

8.2.1.11 Waking with alarm clock set before child wets compared to waking with alarm clock set 2 to 3 hours after child goes to bed for children with monosymptomatic NE

One randomised controlled trial **El Anany (1999)**⁴⁷ compared waking with alarm clock set before child wets to waking with alarm clock set 2 to 3 hours after child goes to bed. **El Anany (1999)**⁴⁷ considered children with monosymptomatic NE.

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Table 8-11: Waking with alarm clock set before child wets compared to waking with alarm clock set 2 to 3 hours after child goes to bed - Clinical summary of findings

Outcome	Alarm clock set before child wets	Alarm clock set 2-3 hours after child goes to bed	Relative risk (95% CI)	Absolute effect	Quality
Dry for 14 consecutive nights in first month	54/70 (77.1%)	34/55 (61.8%)	RR 1.25 (0.98 to 1.59)	154 more per 1000 (from 12 fewer to 365 more)	VERY LOW
Number of children who relapsed after 3 months	8/54 (14.8%)	3/34 (8.8%)	RR 1.68 (0.48 to 5.89)	60 more per 1000 (from 46 fewer to 430 more)	VERY LOW
Number of children who relapsed after 6 months	13/54 (24.1%)	5/34 (14.7%)	RR 1.64 (0.64 to 4.18)	94 more per 1000 (from 53 fewer to 467 more)	VERY LOW

8.2.2 Evidence statements

No evidence was found on the clinical and cost effectiveness of lifting.

Random waking

Studies include children with bedwetting and possible daytime symptoms

Turner (1970)¹⁵⁰

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with random waking and children treated with placebo tablet. Relative risk 0.28, 95% CI 0.04, 2.26. Children had a mean age of 7.5 years and had 4 weeks of treatment.
- One study showed there was no statistically significant difference in the number of wet nights per week at the end of treatment between children treated with random waking and children treated with placebo tablet. Mean difference -0.99, 95% CI -2.54, 0.56. Children had a mean age of 7.5 years and had 4 weeks of treatment.

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with random waking and children treated with an enuresis alarm. Relative risk 0.33, 95% CI 0.04, 2.85. Children had a mean age of 7.5 years and had 4 weeks of treatment.
- One study showed there was no statistically significant difference in the mean number of wet nights per week at the end of treatment between children treated with random waking and children treated with an enuresis alarm. Mean difference 0.33, 95% CI -1.23, 1.89. Children had a mean age of 7.5 years and had 4 weeks of treatment.

Fournier (1987)⁶⁰

- One study showed children treated with random waking had 1.7 fewer wet nights per week at the end of treatment compared to children treated with placebo tablet. Children had a mean age of 8.5 years and had 6 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed children treated with imipramine had 1.4 fewer wet nights per week at the end of treatment compared to children treated with random waking. Children had a mean age of 8.5 years and had 6 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed children treated with an enuresis alarm had 0.8 fewer wet nights per week compared to children treated with random waking. Children had a mean age of 8.5 years and had 6 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed children treated with an enuresis alarm and imipramine had 2.3 fewer wet nights per week compared to children treated with random waking. Children had a mean age of 8.5 years and had 6 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Waking

Studies include children with bedwetting and possible daytime symptoms

Baker (1969) ⁷

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with waking and star charts and children who had no treatment. Relative risk 5, 95% CI 0.26, 95.61. Children had a median age of 8 years and had 10 weeks of treatment.
- One study showed children treated with waking and star charts had 2.8 fewer wet nights per week compared to children who had no treatment. Children had a median age of 8 years and had 10 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed children treated with an enuresis alarm were more likely to achieved 14 consecutive dry nights compared to children treated with waking and star charts. Relative risk 0.18, 95% CI 0.05, 0.68. Children had a median age of 8 years and had 10 weeks of treatment.
- One study showed children treated with an enuresis alarm had 1.3 fewer wet nights per week compared to children treated with waking and star charts. Children had a median age of 8 years and had 10 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Bhatia (1990) ¹²

- One study showed that children treated with imipramine were more likely to achieve 14 consecutive dry nights compared to children treated with waking combined with fluid restriction and parents avoiding punishment of children and placebo. Relative risk 0.33 95% CI 0.13, 0.86. Children had an age range of 4 to 12 years and treatment was for 6 weeks.

Waking (part of a 3 step program)

Studies included children with bedwetting and possible daytime symptoms

lester (1991)⁷⁴

- One study showed children treated with waking (part of a 3 step program) were more likely to achieve 14 consecutive dry nights compared to children treated with imipramine. Relative risk 1.71, 95% CI 1.07, 2.74. Children had an age range of 6 to 11 years and were treated for 6 months.
- One study showed there was no statistically significant difference in the number of children who relapsed at 12 months between children treated with waking (part of a 3 step program) and children treated with imipramine. Relative risk 0.58, 95% CI 0.09, 3.69. Children had an age range of 6 to 11 years and were treated for 6 months.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with waking (part of a 3 step program) and children treated with motivational therapy and 3 step program. Relative risk 0.79, 95% CI 0.62, 1.01. Children had an age range of 6 to 11 years and were treated for 6 months.
- One study showed there was no statistically significant difference in the number of children who relapsed at 12 months between children treated with waking (part of a 3 step program) and children treated with motivational therapy and 3 step program. Relative risk 2.25, 95% CI 0.4, 12.69. Children had an age range of 6 to 11 years and were treated for 6 months.

Waking

Studies with children with monosymptomatic NE

El Anany (1999)⁴⁷

- For children with bedwetting one study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights in the first month between children treated with waking with alarm clock set before the child wets and children treated with waking with alarm clock set 2 to 3 hours after the child goes to bed. Relative risk 1.25, 95% CI 0.98, 1.59. Children had a mean age of 13.23 (children treated with alarm set before wetting) and 12.49 (children treated with alarm set 2 to 3 hours after bed) and had 4 months of treatment.
- For children with bedwetting one study showed there was no statistically significant difference in the number of children who relapsed after 3 months between children treated with waking with alarm clock set before the child

wets and children treated with waking with alarm clock set 2 to 3 hours after the child goes to bed. Relative risk 1.68, 95% CI 0.48, 5.89. Children had a mean age of 13.23 (children treated with alarm set before wetting) and 12.49 (children treated with alarm set 2 to 3 hours after bed) and had 4 months of treatment.

- For children with bedwetting one study showed there was no statistically significant difference in the number of children who relapsed by 6 month follow up between children treated with waking with alarm clock set before the child wets and children treated with waking with alarm clock set 2 to 3 hours after the child goes to bed. Relative risk 1.64, 95% CI 0.64, 4.18. Children had a mean age of 13.23 (children treated with alarm set before wetting) and 12.49 (children treated with alarm set 2 to 3 hours after bed) and had 4 months of treatment.

8.2.3 Evidence to recommendations

Relative values of different outcomes

The GDG considered that achieving and maintaining dryness is the outcome wanted by children and families. The GDG recognized however that families are also likely to need strategies that allow them to achieve dryness on a short term basis such as when away from home, on holiday etc

Trade off between clinical benefit and harms

No evidence of harms was identified.

Economic considerations

No economic evidence was identified.

Quality of evidence (this includes clinical and economic)

No evidence on lifting was found.

The evidence on waking was of very low quality, from small trials with wide confidence intervals, inadequately powered to show a difference in the treatment effects. Some RCTs did not provide statistical data. Comparison treatments were not always equivalent e.g. one RCT had delivered interventions for different lengths of time and two RCTs did not give enough time (only 4 or 6 weeks) for comparison treatment (enuresis alarm) to be fully effective. One RCT had a high drop out rate.

Other considerations

The GDG made a distinction between lifting and waiting as measures which families may use managing bedwetting e.g. when away from home and lifting and waking as measures to help achieve dryness. The GDG considered that lifting without waking was potentially counterproductive as the child does not learn to recognise the sensation of a full bladder. For this reason the GDG were reluctant to consider that lifting without waking had a place even in short term management but did agree that at times families might use it.

There was some evidence waking may increase the number of dry nights.

The studies suggest that other treatments (imipramine, enuresis alarms, enuresis alarm and imipramine) are more effective than waking. The evidence shows positively no difference between the two types of waking (at a set time or before the child wets). In combination with other treatments waking was shown to have some effect, more dry nights compared to no treatment however it was unclear which part of the combination was effective. Waking in combination with other behavioural techniques was not shown to be more effective than enuresis alarms. The GDG did not consider there was enough evidence to support the use of waking in combination with other treatments.

The health care professionals on the GDG stated that waking may be useful as a temporary measure but should not be used for treatment. GDG members reported that young people who have not found success with any other treatment do sometimes use waking to ensure dry nights and should not be dissuaded from this.

8.2.4 Recommendations

8.2.4.1 Offer advice on waking and lifting during the night as follows:

- Neither waking nor lifting, at regular times or randomly, for children with bedwetting will promote long-term dryness.
- Waking by parents or carers, either at regular times or randomly, should be used only as a practical measure in the short-term management of bedwetting.
- Young people with bedwetting that has not responded to treatment may find self-instigated waking a useful management strategy.[1.6.1]

9 Bladder training and retention control training for the management of bedwetting

9.1 Introduction

Although terms bladder training and retention control training are used by healthcare professionals working in the area of childhood wetting there is currently no universally agreed definition of bladder training or retention control training and the evidence in this area was difficult to evaluate. Both terms seem to describe the aim of treatment rather than a specific programme. Highman (1953) and Muellner (1960) introduced the idea that bladder training, understood as drinking and practice in holding urine, might be a useful treatment to improve enuresis. Retention control training most commonly means that children are encouraged to hold voiding as long as possible once a day as a means of expanding their bladder capacity. In the evidence found in this area both strategies are combined with other management strategies but the components are poorly described and are combined in different ways.

The following interventions were included in the evidence review on the effectiveness of bladder training and retention control training: retention control training compared to no treatment; retention control training compared to other treatments; retention control training compared to combination of treatments; bladder training compared to no treatment; bladder training compared to other treatments; bladder training compared to combination of treatments.

9.2 What is the clinical and cost effectiveness of bladder training and retention control training for children and young people under 19 years who have bedwetting?

9.2.1 Evidence review

A brief description of each intervention is included for clarity and understanding.

9.2.1.1 Retention control training and placebo compared to desmopressin

One randomised controlled trial **Kahan (1998)**⁷⁹ compared retention control training and a placebo to desmopressin. In the trial children in the retention control training group were 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 wiliness and 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.

Table 9-1: Retention control training and placebo compared to desmopressin - Clinical summary of findings

Outcome	RCT and placebo	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	12/75 (16%)	31/76 (40.8%)	RR 0.39 (0.22 to 0.7)	249 fewer per 1000 (from 122 fewer to 318 fewer)	LOW
Mean number of wet nights per week at the end of treatment	75	76	-	MD -1.2 (-1.84 to -0.56)	VERY LOW
Mean number of wet nights per week at follow up	75	76	-	MD -1.4 (-2.04 to -0.76)	LOW
Number of children who relapsed	6/12 (50%)	18/31 (58.1%)	RR 0.86 (0.45 to 1.63)	81 fewer per 1000 (from 320 fewer to 366 more)	VERY LOW
Number of children who dropped out	1/75 (1.3%)	0/76 (0%)	RR 3.04 (0.13 to 73.45)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

9.2.1.2 Retention control training and placebo compared to retention control training and desmopressin

One randomised controlled trial **Kahan (1998)**⁷⁹ compared retention control training and desmopressin to retention control training and placebo. In the trial children in the retention control training group were 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 wiliness and 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.

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Table 9-2: Retention control training and placebo compared to retention control training and desmopressin - Clinical summary of findings

Outcome	RCT and placebo	RCT and desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	12/75 (16%)	22/70 (31.4%)	RR 0.51 (0.27 to 0.95)	154 fewer per 1000 (from 16 fewer to 229 fewer)	VERY LOW
Mean number of wet nights per week at the end of treatment	75	70	-	MD 0.3 (-0.38 to 0.98)	VERY LOW
Mean number of wet nights per week at follow up	75	70	-	MD 0.7 (0.06 to 1.34)	VERY LOW
Number of children who relapsed	6/12 (50%)	18/22 (81.8%)	RR 0.61 (0.34 to 1.11)	319 fewer per 1000 (from 540 fewer to 90 more)	VERY LOW
Number of children who dropped out	1/75 (1.3%)	6/70 (8.6%)	RR 0.16 (0.02 to 1.26)	72 fewer per 1000 (from 84 fewer to 22 more)	VERY LOW

9.2.1.3 Stop start training compared to an enuresis alarm

One randomised controlled trial, **Bennett (1985)**¹¹, compared bladder training to enuresis alarms. Stop start training was described as sphincter muscle exercises.

Table 9-3: Stop start training compared to an enuresis alarm - Clinical summary of findings

Outcome	Stop start training	Enuresis alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	2/12 (16.7%)	4/9 (44.4%)	RR 0.38 (0.09 to 1.62)	275 fewer per 1000 (from 404 fewer to 275 more)	VERY LOW

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Mean number of wet nights per week at the end of treatment	12	9	-	MD 2.25 (0.3 to 4.2)	VERY LOW
Number of children who dropped out	11/23 (47.8%)	9/18 (50%)	RR 0.96 (0.51 to 1.79)	20 fewer per 1000 (from 245 fewer to 395 more)	VERY LOW

9.2.1.4 *Stop start training compared to dry bed training with an enuresis alarm*

One randomised controlled trial, **Bennett (1985)**¹¹ compared bladder training to dry bed training with an enuresis alarm. Stop start training was described as sphincter muscle exercises.

Table 9-4: Stop start training compared to dry bed training with an enuresis alarm - Clinical summary of findings

Outcome	Stop start training	DBT with an alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	2/12 (16.7%)	5/10 (50%)	RR 0.33 (0.08 to 1.36)	335 fewer per 1000 (from 460 fewer to 180 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	12	10	-	MD 1.85 (0 to 3.7)	VERY LOW
Number of children who dropped out	11/23 (47.8%)	10/20 (50%)	RR 0.96 (0.52 to 1.76)	20 fewer per 1000 (from 240 fewer to 380 more)	VERY LOW

9.2.1.5 *Stop start training compared to star charts*

One randomised controlled trial, **Bennett (1985)**¹¹ compared bladder training to star charts. Stop start training was describe as sphincter muscle exercises.

Table 9-5: Stop start training compared to star charts - Clinical summary of findings

Outcome	Stop start training	Star charts	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	2/12 (16.7%)	0/9 (0%)	RR 3.85 (0.21 to 71.48)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

Mean number of wet nights per week at the end of treatment	12	9	-	MD -1.9 (-3.67 to -0.13)	VERY LOW
Number of children who dropped out	11/23 (47.8%)	3/12 (25%)	RR 1.91 (0.66 to 5.57)	227 more per 1000 (from 85 fewer to 1000 more)	VERY LOW

9.2.1.6 Bladder training (part of a 3 step program) compared to imipramine

One randomised controlled trial, **lester (1991)**⁷⁴ compared bladder training (part of a 3 step program) to imipramine. 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.

Table 9-6: Bladder training (part of a 3 step program) compared to imipramine - Clinical summary of findings

Outcome	Bladder training	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	24/36 (66.7%)	14/36 (38.9%)	RR 1.71 (1.07 to 2.74)	276 more per 1000 (from 27 more to 677 more)	VERY LOW
Number of children who relapsed after 12 months	2/24 (8.3%)	2/14 (14.3%)	RR 0.58 (0.09 to 3.69)	60 fewer per 1000 (from 130 fewer to 385 more)	VERY LOW

9.2.1.7 Bladder training (part of a 3 step program) compared to motivational therapy and 3 step program

One randomised controlled trial, **lester (1991)**⁷⁴ compared bladder training (part of a 3 step program) to motivational therapy and a 3 step program. Children in the bladder training group took part in a three step program which was 1) reassurance to the parents and trying 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 motivational therapy group had the 3 step program as described and motivational therapy where child, in a group, discussed their problems with a psychiatrist.

Table 9-7: Bladder training (part of a 3 step program) compared to motivational therapy and 3 step program - Clinical summary of findings

Outcome	Bladder training	Motivational therapy	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	24/36 (66.7%)	81/96 (84.4%)	RR 0.79 (0.62 to 1.01)	177 fewer per 1000 (from 321 fewer to 8 more)	VERY LOW
Number of children who relapsed after 12 months	2/24 (8.3%)	3/81 (3.7%)	RR 2.25 (0.4 to 12.69)	46 more per 1000 (from 22 fewer to 433 more)	VERY LOW

9.2.1.8 Retention control training compared to no treatment for children with bedwetting

One randomised controlled trial, **Harris (1977)**⁶⁹ compared retention control training to no treatment. **Harris (1977)**⁶⁹ considered only children with bedwetting. Retention control training was described as 5 nights in a camp, then 30 days with parents, 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 they 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.

Table 9-8: Retention control training compared to waiting list - Clinical summary of findings

Outcome	Retention control training	Waiting list	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment (no sd)	9	9	-	not pooled	VERY LOW

9.2.1.9 Retention control training compared to desmopressin for children with monosymptomatic NE and severe wetting

One randomised controlled trial, **Hamano (2000)**⁶⁸ compared retention control training to desmopressin. **Hamano (2000)**⁶⁸ considered children with monosymptomatic NE and severe wetting. Retention control training was described as when children were encouraged by their parents to hold voiding for as long as possible once a day.

Table 9-9: Retention control training compared to desmopressin - Clinical summary of findings

Outcome	Retention control training	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	14/60 (23.3%)	21/54 (38.9%)	RR 0.6 (0.34 to 1.06)	156 fewer per 1000 (from 257 fewer to 23 more)	VERY LOW

9.2.2 Network Meta-Analysis

Retention control training and stop-start training were amongst the interventions included in a network meta-analysis of interventions used for nocturnal enuresis. The summary of results of this analysis is presented in chapter 24 and a detailed description of the analysis is presented in appendix F. If studies did not meet the inclusion criteria of the network meta-analysis protocol as stated in appendix F they were not included in the network meta-analysis

9.2.3 Evidence statements

Retention control training

Studies with children with bedwetting and possible daytime symptoms

Kahan (1998)⁷⁹

- One study showed children treated with desmopressin were more likely to achieve 14 consecutive dry nights compared to children treated with retention control training and placebo. Relative risk 0.39, 95% CI 0.22, 0.7. Children had an age range of 8 to 14 years and were treated for 8 weeks.

- One study showed children treated with retention control training and placebo had fewer wet nights per week at the end of treatment compared to children treated with desmopressin. Mean difference -1.2, 95% -1.84, -0.56. Children had an age range of 8 to 14 years and were treated for 8 weeks.
- One study showed children treated with retention control training and placebo had fewer wet nights per week at follow up compared to children treated with desmopressin. Mean difference -1.4, 95% CI -2.04, -0.76. Children had an age range of 8 to 14 years and were treated for 8 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with retention control training and children treated with desmopressin. Relative risk 0.86, 95% CI 0.45, 1.63. Children had an age range of 8 to 14 years and were treated for 8 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with retention control training and children treated with desmopressin. Relative risk 3.04, 95% CI 0.13, 73.45. Children had an age range of 8 to 14 years and were treated for 8 weeks.
- One study showed children treated with retention control training and desmopressin were more likely to achieve 14 consecutive dry nights compared to children treated with retention control training and placebo. Relative risk 0.51, 95% CI 0.27, 0.95. Children had an age range of 8 to 14 years and were treated for 8 weeks.
- One study showed there was no statistically significant difference in the mean number of wet nights per week at the end of treatment between children treated with retention control training and desmopressin and children treated with retention control training and placebo. Mean difference 0.3, 95% CI -0.38, 0.98. Children had an age range of 8 to 14 years and were treated for 8 weeks.
- One study showed children treated with retention control training and desmopressin had fewer wet nights per week at follow up compared to children treated with retention control training and placebo. Mean difference 0.7, 95% CI 0.06, 1.34. Children had an age range of 8 to 14 years and were treated for 8 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with retention

control training and desmopressin and children treated with retention control training and placebo. Relative risk 0.61, 95% CI 0.34, 1.11. Children had an age range of 8 to 14 years and were treated for 8 weeks.

- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with retention control training and desmopressin and children treated with retention control training and placebo. Relative risk 0.16, 95% CI 0.02, 1.26. Children had an age range of 8 to 14 years and were treated for 8 weeks.

Stop start training

Studies included children with bedwetting and possible daytime symptoms

Bennett (1985) ¹¹

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the number of children treated with stop start training and the number of children treated with an enuresis alarm. Relative risk 0.38, 95% CI 0.09, 1.62. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed children treated with an enuresis alarm had fewer wet nights per week at the end of treatment compared to children treated with stop start training. Mean difference 2.25, 95% CI 0.3, 4.2. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with stop start training and children treated with enuresis alarms. Relative risk 0.96, 95% CI 0.51, 1.79. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the number of children treated with stop start training and the number of children treated with dry bed training and an enuresis alarm. Relative risk 0.33, 95% CI 0.08, 1.36. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed children treated with dry bed training and an enuresis alarm had fewer wet nights per week at the end of treatment compared to

children treated with stop start training. Mean difference 1.85, 95% CI 0, 3.7. Children had a mean age of 8.5 years and had 12 weeks of treatment.

- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with stop start training and children treated with dry bed training. Relative risk 0.96, 95% CI 0.52, 1.76. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the number of children treated with stop start training and the number of children who had star charts. Relative risk 3.85, 95% CI 0.21, 71.48. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study children treated with stop start training had fewer wet nights per week at the end of treatment compared to children who had star charts. Mean difference -1.9, 95% CI -3.67, -0.13. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with stop start training and children treated with star charts. Relative risk 1.91, 95% CI 0.66, 5.57. Children had a mean age of 8.5 years and had 12 weeks of treatment.

Bladder training (part of a 3 step program)

Studies include children with bedwetting and possible daytime symptoms

Iester (1991) ⁷⁴

- One study showed children treated with bladder training (part of a 3 step program) were more likely to achieve 14 consecutive dry nights compared to children treated with imipramine. Relative risk 1.71, 95% CI 1.07, 2.74. Children had an age range of 6 to 11 years and were treated for 6 months.
- One study showed there was no statistically significant difference in the number of children who relapsed at 12 months between children treated with bladder training (part of a 3 step program) and children treated with imipramine. Relative risk 0.58, 95% CI 0.09, 3.69. Children had an age range of 6 to 11 years and were treated for 6 months.

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with bladder training (part of a 3 step program) and children treated with motivational therapy and 3 step program. Relative risk 0.79, 95% CI 0.62, 1.01. Children had an age range of 6 to 11 years and were treated for 6 months.
- One study showed there was no statistically significant difference in the number of children who relapsed at 12 months between children treated with bladder training (part of a 3 step program) and children treated with motivational therapy and 3 step program. Relative risk 2.25, 95% CI 0.4, 12.69. Children had an age range of 6 to 11 years and were treated for 6 months.

Retention control training

Studies include children with bedwetting only

Harris (1977) ⁶⁹

- For children with bedwetting one study showed children treated with retention control training had 2.4 fewer wet nights per week at the end of training compared to children who had no treatment. Children had a mean age of 8.8 and 9.2 years and had treatment for 35 days. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Retention control training

Studies include children with monosymptomatic NE and severe wetting

Hamano (2000) ⁶⁸

- For children with bedwetting and severe wetting one study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with retention control training and children treated with desmopressin. Relative risk 0.6, 95% CI 0.34, 1.06. Children had a mean of 9.2 and 9.4 years and had 12 weeks of treatment.

NCGC network meta-analysis (see appendix F)

For children with bedwetting and possible daytime symptoms

- The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with stop start training and no treatment / placebo. Relative risk 6.245, 95% CI 1.267, 9.085. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.

For children with bedwetting only

- The NCGC NMA showed there was no statistically significant difference in the number of children who achieved a full response between children treated with retention control training and alarm and no treatment / placebo. Relative risk 3.484, 95% CI 0.224, 9.031. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.
- The NCGC NMA showed there was no statistically significant difference in the number of children who experienced a recurrence of bedwetting at 6 months between children treated with retention control training and alarm and no treatment / placebo. Relative risk 0.024, 95% CI 0.001, 1.4. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.

For estimates of treatment effect relative to other active comparators, please see section 24.4 in chapter 24.

9.2.4 Evidence to recommendations

Relative values of different outcomes

The GDG considered the children and parents or carers starting treatment for bedwetting were seeking an outcome of sustained dryness. A number of different outcomes were used to capture this: the outcome of 14 consecutive dry nights, reduction in wet nights and the mean number of wet nights allow evaluation of the effectiveness of treatment. Follow up rates where available can indicate sustained dryness.

Trade off between clinical benefit and harms

No evidence of harms was identified in the studies but the GDG considered that there is expert opinion that interrupting voiding or encouraging infrequent micturition may promote voiding dysfunction.

Economic considerations

No economic evidence was available to determine the cost-effectiveness of retention control or bladder training. Other than consultation time with health care

professionals, these interventions alone cost nothing to use, however the evidence shows that they are not very effective either. If most children are going to require further treatment with other interventions anyway, it would not be cost-effective to spend time trialing retention control or bladder training. If there are harms, such as voiding dysfunction, associated with interrupting voiding or frequent micturition, then these interventions are even more unlikely to be cost-effective.

Quality of evidence (this includes clinical and economic)

All studies described retention control training or bladder training differently. The RCTs had wide confidence intervals and were not powered enough to detect differences in the treatment effects. Older studies did not include adequate statistical information for analysis. High drop out rates were reported and in the trial of stop- start training and imipramine treatments were given for different lengths of time in different arms of trial..

Other considerations

The GDG did not believe that the evidence for the interventions was sufficient to recommend their use ahead of other treatments.

The evidence indicated that programmes might be more effective than no treatment but than when compared with standard treatments such as desmopressin they were less effective.

The studies all described bladder training or retention control training slightly differently. The interventions included in these trials were considered to be complex interventions with multiple components but there was inadequate description of the individual components, the rationale for combining them and evaluation of what actually happened in the trials. The terminology of bladder training and retention control training was so imprecise that the GDG considered it unhelpful to use it. The GDG considered that the programmes described appeared to have as a core component the interruption of voiding once voiding had started. The GDG were uncomfortable with the use of stop- start interventions considering that this may be unhelpful from a physiological perspective. This technique is useful for adults with pelvic floor weakness but small bladder capacity is a more likely problem for children. The GDG did not believe that teaching children to hold on in the day results in holding on when asleep. Other components of the interventions such as reduction in fluid intake before bed are part of usual advice to children with bedwetting.

9.2.5 Recommendations

- 9.2.5.1 *Do not use strategies that recommend the interruption of urinary stream or encourage infrequent passing of urine during the day [1.14.1]*

10 Star Charts in the management of bedwetting

10.1 Introduction

Star charts and rewards systems are the giving of some reward either for a dry night or for the correct toileting behaviour, regardless of the child actually being dry overnight. The rewards can range from stars on charts in the child's room or in a family room to pocket money or time earned for a preferred activity such as gaming. Star charts are used in wide variety of settings to reward children for good behaviour e.g. educational settings. They are therefore often familiar to children and parents or carers.

For this evidence review studies of star charts or reward systems in the treatment of bedwetting were systematically searched for. Evidence for the effectiveness of star charts only was identified. The GDG decided that although the evidence reviewed considered star charts, the recommendations should be worded with reward systems, where either a star or mark on a chart indicates the desired outcome was achieved or if the parent / carer feels a different type of reward would be more appropriate or effective then this could be done at the parent / carer's discretion. The important factor in the choice of rewards is that they are something that motivates the child. No-one wants to work hard for unwanted or unvalued rewards.

10.2 What is the clinical and cost effectiveness of the use of star charts for children and young people under 19 years who have bedwetting?

10.2.1 Evidence review

10.2.1.1 Star chart compared to enuresis alarm

One randomised controlled trial, **Bennett (1985)**¹¹ compared star chart to enuresis alarm. Stars were given as a reward for a dry night. The trial outcomes were the number of children which achieved 14 consecutive dry nights, the mean number of wet nights in the last week of treatment and the number of children who dropped out.

Table 10-1: Star chart compared to enuresis alarms - Clinical summary of findings

Outcome	Star chart	Alarms	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	0/9 (0%)	4/9 (44.4%)	RR 0.11 (0.01 to 1.8)	395 fewer per 1000 (from 440 fewer to 355 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	9	9	-	MD 4.15 (2.54 to 5.76)	LOW
Number of children who dropped out	3/12 (25%)	9/18 (50%)	RR 0.5 (0.17 to 1.48)	250 fewer per 1000 (from 415 fewer to 240 more)	VERY LOW

10.2.1.2 *Star chart with rewards and enuresis alarm*⁷

One randomised controlled trial, **Van Londen (1993)**¹⁵⁶, a randomised controlled trial evaluated two types of star charts combined with an enuresis alarm. The mean age was 8.6 years and the length of treatment was 20 weeks. The two star charts were (1) two reward stickers were given immediately for correct behaviour of waking to the enuresis alarm within 3 minutes, going to the toilet after, returning to bed and resetting the enuresis alarm, and one sticker was asked for as a charge for incorrect behavior (i.e if child did not wake to the alarm) 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.

Table 10-2: Star chart with rewards and enuresis alarm⁸ - Clinical summary of findings

Outcome	Star chart with reward for correct behaviour	Star chart with reward for dry night	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	37/38 (97.4%)	33/39 (84.6%)	RR 1.15 (1 to 1.33)	127 more per 1,000	MODERATE

⁷ In the Van Londen study, Two reward stickers were given immediately for waking up to the enuresis alarm or one sticker asked for as a charge for not waking to the enuresis alarm combined with an enuresis alarm compared to star chart with 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 combined with an enuresis alarm.

⁸ Van Londen study as described above.

Number of relapses at 2.5 years	10/37 (27%)	15/33 (45.5%)	RR 0.59 (0.31 to 1.14)	186 fewer per 1,000	VERY LOW
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10.2.1.3 Star chart compared to dry bed training and an enuresis alarm

One randomised controlled trial, **Bennett (1985)**¹¹ compared star charts to dry bed training with an enuresis alarm. Stars were given for dry nights. The trial outcomes were the number of children who achieved 14 consecutive dry nights, the mean number of wet nights per week at the end of treatment and the number of children who dropped out.

Table 10-6: Star chart compared to dry bed training - Clinical summary of findings

Outcome	Star chart	Dry bed training	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	0/9 (0%)	5/10 (50%)	RR 0.1 (0.01 to 1.59)	450 fewer per 1000 (from 495 fewer to 295 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	9	10	-	MD 3.75 (2.27 to 5.23)	LOW
Number of children who dropped out	3/12 (25%)	10/19 (52.6%)	RR 0.47 (0.16 to 1.38)	279 fewer per 1000 (from 442 fewer to 200 more)	VERY LOW

10.2.1.4 Star chart and placebo compared to star chart and imipramine

One randomised controlled trial, **Maxwell (1971)**¹⁰⁰ compared star charts and placebo to star charts and imipramine. Stars (coloured blue) were given for a dry night, after 3 dry nights in a row an extra gold star was given.

Table 10-4: Star chart and placebo compared to star chart and imipramine - Clinical summary of findings

Outcome	Star chart and placebo	Star chart and imipramine	Relative risk (95% CI)	Absolute effect	Quality
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Mean number of wet nights per month at the end of treatment	125	125	-	MD 3.4 (1.27 to 5.53)	LOW
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10.2.1.5 Star chart and waking compared to no treatment

One randomised controlled trial, **Baker (1969)**⁷ compared star charts and waking to no treatment. The trial outcomes were the number of children who achieved 14 consecutive dry nights and the mean number of wet nights per week in the last 3 weeks of treatment. 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.

Table 10-5: Star chart and waking compared to no treatment - Clinical summary of findings

Outcome	Star chart and waking	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	2/14 (14.3%)	0/14 (0%)	RR 5 (0.26 to 95.61)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Mean number of wet nights per week in the last 3 weeks of treatment	10	10	-	not pooled	VERY LOW

10.2.1.6 Star chart and waking compared to enuresis alarm

One randomised controlled trial, **Baker (1969)**⁷ compared star charts and waking to enuresis alarms. The trial outcomes were the number of children who achieved 14 consecutive dry nights and the mean number of wet nights per week in the last 3 weeks of treatment. Star charts were used to keep a record of the child's progress.

Table 10-6: Star chart and waking compared to enuresis alarm - Clinical summary of findings

Outcome	Star chart and waking	Alarm	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	2/14 (14.3%)	11/14 (78.6%)	RR 0.18 (0.05 to 0.68)	645 fewer per 1000 (from 252 fewer to 747 fewer)	LOW
Mean number of wet nights per weeks in the last 3 weeks of treatment	10	10	-	not pooled	VERY LOW

10.2.1.7 Star chart compared to no treatment for children with severe wetting

One randomised controlled trial, **Ronen (1992)**¹³¹ compared star chart to a waiting list group. **Ronen (1992)**¹³¹ considered children with severe wetting. Stars were given as a reward for a dry night.

Table 10-7: Star chart compared to no treatment - Clinical summary of findings

Outcome	Star chart	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who were dry for 14 consecutive nights	6/20 (30%)	0/18 (0%)	RR 11.76 (0.71 to 195.11)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Mean number of wet nights in 3 weeks at the end of treatment	14	16	-	MD -13.89 (-19.25 to -8.53)	LOW
Number of children who dropped out	6/20 (30%)	11/18 (61.1%)	RR 0.49 (0.23 to 1.05)	312 fewer per 1000 (from 470 fewer to 31 more)	VERY LOW

10.2.1.8 Star chart compared to enuresis alarm for children with severe wetting

One randomised controlled trial, **Ronen (1992)**¹³¹ compared star chart to enuresis alarm. **Ronen (1992)**¹³¹ considered children with severe wetting; stars were given as a reward for a dry night.

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Table 10-8: Star charts compared to enuresis alarms - Clinical summary of findings

Outcome	Star chart	Alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	6/20 (30%)	12/19 (63.2%)	RR 0.47 (0.22 to 1.01)	335 fewer per 1000 (from 493 fewer to 6 more)	VERY LOW
Mean number of wet nights in 3 weeks at the end of treatment	14	15	-	MD 2.1 (-1.95 to 6.15)	VERY LOW
Number of children who failed or relapsed after 6 months	8/14 (57.1%)	9/15 (60%)	RR 0.95 (0.52 to 1.76)	30 fewer per 1000 (from 288 fewer to 456 more)	VERY LOW
Number of children who dropped out	6/20 (30%)	4/19 (21.1%)	RR 1.42 (0.48 to 4.27)	89 more per 1000 (from 110 fewer to 690 more)	VERY LOW

10.2.1.9 Star chart compared to cognitive behaviour therapy for children with severe wetting

One randomised controlled trial, **Ronen (1992)**¹³¹ compared star chart to cognitive behaviour therapy. **Ronen (1992)**¹³¹ considered children with severe wetting. Stars were given as a reward for a dry night; cognitive behaviour therapy was 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”.

Table 10-9: Star chart compared to cognitive behavioural therapy - Clinical summary of findings

Outcome	Star chart	CBT	Relative risk (95% CI)	Absolute effect	Quality
Number of children who were dry for 14 consecutive nights	6/20 (30%)	15/20 (75%)	RR 0.4 (0.2 to 0.82)	450 fewer per 1000 (from 135 fewer to 600 fewer)	VERY LOW
Mean number of wet nights in 3 weeks at the end of treatment	14	18	-	MD 2.3 (-0.9 to 5.5)	VERY LOW

Number of children who failed or relapsed after 6 months	8/14 (57.1%)	3/18 (16.7%)	RR 3.43 (1.11 to 10.59)	406 more per 1000 (from 18 more to 1000 more)	VERY LOW
Number of children who dropped out	6/20 (30%)	2/20 (10%)	RR 3 (0.69 to 13.12)	200 more per 1000 (from 31 fewer to 1000 more)	VERY LOW

10.2.1.10 Star chart compared to unstructured play therapy for children with severe wetting

One randomised controlled trial, **Fava (1981)**⁵⁴ compared star charts to unstructured play therapy. **Fava (1981)**⁵⁴ considered children with severe wetting (children wet every night). The star chart treatment group had a star given by parents on the family calendar, so the whole family could see, for a dry nights, a reward for example pocket money was then given after each star; play therapy was described as “unstructured play therapy; behavioural suggestions were carefully excluded”.

Table 10-10: Star chart compared to play therapy - Clinical summary of findings

Outcome	Star chart	Play therapy	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	8/10 (80%)	1/10 (10%)	RR 8 (1.21 to 52.69)	700 more per 1000 (from 21 more to 1000 more)	VERY LOW
Number of children who failed or relapsed	2/10 (20%)	9/10 (90%)	RR 0.22 (0.06 to 0.78)	702 fewer per 1000 (from 198 fewer to 846 fewer)	VERY LOW
Number of children who achieved 14 consecutive dry nights (excludes children who were lifted)	6/10 (60%)	1/10 (10%)	RR 6 (0.87 to 41.21)	500 more per 1000 (from 13 fewer to 1000 more)	6/10 (60%)

10.2.2 Network Meta-Analysis

Star charts were amongst the interventions included in a network meta-analyses of interventions used for nocturnal enuresis. The summary of results of this analysis is

presented in chapter 24 and a detailed description of the analysis is presented in appendix F. If studies did not meet the inclusion criteria of the network meta-analysis protocol as stated in appendix F they were not included in the network meta-analysis

10.2.3 Evidence statements

Studies included children with bedwetting and possible daytime symptoms

Bennett (1985)¹¹

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with star charts and children treated with an enuresis alarm. Relative risk 0.11, 95% CI 0.01, 1.8. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed children treated with an enuresis alarm had fewer wet nights per week at the end of treatment compared to children treated with star charts. Mean difference 4.15, 95% CI 2.54, 5.76. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with star charts and children treated with enuresis alarms. Relative risk 0.5, 95% CI 0.17, 1.48. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed children treated with dry bed training and an enuresis alarm had fewer wet nights per week at the end of treatment compared to children treated with star charts. Mean difference 3.75, 95% CI 2.27, 5.23. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed children treated with stop start training had fewer wet nights per week at the end of treatment compared to children treated with star charts. Mean difference 1.9, 95% CI 0.13, 3.67. Children had a mean age of 8.5 years and had 12 weeks of treatment.

Baker (1969)⁷

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with a star chart and waking and children who had no treatment.

Relative risk 5, 95% CI 0.26, 95.16. Children had a median age of 8 years and treatment was for 10 weeks.

- One study showed children treated with a star chart and waking had 2.8 fewer wet nights per week at the end of treatment compared to children who had no treatment. Children had a median age of 8 years and treatment was for 10 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed children treated with an enuresis alarm were more likely to achieve 14 consecutive dry nights compared to children treated with a star chart and waking. Relative risk 0.18, 95% CI 0.05, 0.68. Children had a median age of 8 years and treatment was for 10 weeks.
- One study showed children treated with an enuresis alarm had 1.3 fewer wet nights per week at the end of treatment compared to children treated with a star chart and waking. Children had a median age of 8 years and treatment was for 10 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Van Londen (1993)¹⁵⁶

- One study showed children treated with an enuresis alarm plus a star chart with rewards for correct behaviour (for waking up to the enuresis alarm within 3 minutes, going to the toilet after, returning to bed and resetting the enuresis alarm) and asking for one sticker to be returned if correct behaviour not demonstrated were more likely to achieve 14 consecutive dry nights compared to children treated with an enuresis alarm plus a star chart with reward for dry night and one sticker to be returned for a wet night. Relative risk 1.15, 95% CI 1, 1.33. Children had a mean age of 8.6 years and the length of treatment was 20 weeks.
- One study showed there was no statistically significant difference in the number of children relapsing at 2.5 years between children treated with an enuresis alarm plus a star chart with rewards for correct behaviour (for waking up to the enuresis alarm within 3 minutes, going to the toilet after, returning to bed and resetting the enuresis alarm) and asking for one sticker to be returned if correct behaviour not demonstrated and children treated with an enuresis alarm plus a star chart with reward for dry night and one sticker to be returned for a wet night. Relative risk 0.59, 95% CI 0.31 to 1.14.

Children had a mean age of 8.6 years and the length of treatment was 20 weeks.

Studies included children with severe wetting

Ronen (1992) ¹³¹

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with star charts and children who had no treatment. Relative risk 11.76, 95% CI 0.71, 195.11. Children had a mean age of 10.05 years and treatment was for 18 weeks.
- One study showed children treated with star charts had fewer wet nights in the last 3 weeks of treatment compared to children who had no treatment. Mean difference -13.89, 95% CI -19.25, -8.53. Children had a mean age of 10.05 years and treatment was for 18 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with star charts and children who had no treatment. Relative risk 0.49, 95% CI 0.23, 1.05. Children had a mean age of 10.05 years and treatment was for 18 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with star charts and children treated with enuresis alarms. Relative risk 0.47, 95% CI 0.22, 1.01. Children had a mean age of 10.05 years and treatment was for 18 weeks.
- One study showed there was no statistically significant difference in the mean number of wet nights in the last 3 weeks of treatments between children treated with star charts and children treated with enuresis alarms. Mean difference 2.1, 95% CI -1.95, 6.15. Children had a mean age of 10.05 years and treatment was for 18 weeks.
- One study showed there was no statistically significant difference in the number of children who failed or relapsed at 6 months between children treated with star charts and children treated with enuresis alarms. Relative risk 0.95, 95% CI 0.52, 1.76. Children had a mean age of 10.05 years and treatment was for 18 weeks.

- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with star charts and children treated with enuresis alarms. Relative risk 1.42, 95% CI 0.48, 4.27. Children had a mean age of 10.05 years and treatment was for 18 weeks.
- One study showed children treated with CBT were more likely to achieve 14 consecutive dry nights compared to children treated with star charts. Relative risk 0.4, 95% CI 0.2, 0.82. Children had a mean age of 10.05 years and treatment was for 18 weeks.
- One study showed there was no statistically significant difference in the mean number of wet nights in the last 3 weeks of treatments between children treated with star charts and children treated with CBT. Mean difference 2.3, 95% CI -0.9, 5.5. Children had a mean age of 10.05 years and treatment was for 18 weeks.
- One study showed children treated with star charts were more likely to fail or relapse at 6 months compared to children treated with counselling. Relative risk 3.43, 95% CI 1.11, 10.59. Children had a mean age of 10.05 years and treatment was for 18 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with star charts and children treated with CBT. Relative risk 3, 95% CI 0.69, 13.12. Children had a mean age of 10.05 years and treatment was for 18 weeks.

Studies include children with bedwetting only

Maxwell (1971)¹⁰⁰

- One study showed children treated with star chart and imipramine had fewer wet nights per week compared to children treated with star chart and placebo. Mean difference 3.4, 95% CI 1.27, 5.53. Children had an age range of 5 to 12 years and treatment was for 4 weeks.

Fava (1981)⁵⁴

- One study showed children treated with a star chart were more likely to achieve 14 consecutive dry nights compared to children treated with unstructured play therapy. Relative risk 8, 95% CI 1.21, 52.69. Children had a mean age of 8 years and had treatment for 3 months. Two children in the star chart group had to be lifted as treatment was unsuccessful after 15 nights.

- One study showed children treated with unstructured play therapy were more likely to fail or relapse 1 year after treatment compared to children treated with star charts. Relative risk 0.22, 95% CI 0.06, 0.78. Children had a mean age of 8 years and had treatment for 3 months.
- One study showed children treated with star chart were more likely achieved 14 consecutive dry nights compared to children treated with unstructured play therapy. Relative risk 6, 95% CI 0.87, 41.21. Children had a mean age of 8 years and had treatment for 3 months. Evidence statement for children who only received star charts (excludes two children who were also lifted)

NCGC network meta-analysis (see appendix F)

- **The NCGC NMA showed there was no statistically significant difference in the number of children who achieved a full response between children treated with star chart and no treatment / placebo. Relative risk 1.891, 95% CI 0.282, 7.709. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**

For estimates of treatment effect relative to other active comparators, please see section 24.4 in chapter 24.

10.2.4 Evidence to recommendations

Relative values of different outcomes

The GDG considered that children and parents or carers starting treatment for bedwetting were seeking an outcome of sustained dryness. A number of different outcomes were used to capture this: the outcome of 14 consecutive dry nights, reduction in wet nights and the mean number of wet nights allow evaluation of the effectiveness of treatment. Follow up rates where available can indicate sustained dryness.

Trade off between clinical benefit and harms

No evidence of harms was identified.

Economic considerations

No economic evidence was identified, but reward systems, such as star charts, are relatively easy to implement, would represent no cost to the NHS and might be effective as an initial treatment in young children. It is likely that from the perspective of the NHS, reward systems are cost-effective compared to no treatment. However, many children will not achieve complete dryness and will

require a different, potentially costlier intervention. Reward systems may not be appropriate for all children, including older children, therefore they also may require different, potentially costlier treatment.

Quality of evidence (this includes clinical and economic)

Most of the studies were of low or very low quality evidence with wide confidence intervals and are unlikely to have been powered enough to show difference in the treatments

Other considerations

The GDG decided that although the evidence reviewed considered star charts, the recommendations should be worded with reward systems, where either a star or mark on a chart indicates the desired outcome was achieved or if the parent / carer feels a different type of reward would be more appropriate or effective then this could be done at the parent / carer's discretion.

One RCT showed star charts are more effective than unstructured play therapy. The RCT suggests it is not just the interaction with the child which causes dryness but the focus on bedwetting behaviours which leads to success. Three RCTs showed other treatments (dry bed training with an enuresis alarm, CBT, enuresis alarm and stop start training) gave fewer wet nights however there was no difference for 14 dry nights and drop out rates. Reward systems are however easier to implement for most families.

The GDG were impressed by the study by Van London et al (1993) which compared immediate rewards for correct behaviour with delayed rewards for dry nights. The study showed that in children treated with enuresis alarm, immediate rewards for waking are more effective than delayed rewards for dry nights. The GDG considered that the population included in the study (average age 8.6 years) could be expected to respond best reward systems. In the same study, children in each group were penalised, asked to give up previously gained rewards, for either incorrect behaviour or wet nights, respectively. The GDG felt such a penalty was inappropriate and that it was unlikely to have an incremental impact on the effectiveness of reward systems. Thus, the GDG felt it important to discourage parents and carers from using reward systems that penalise or take away previous gained rewards.

The GDG considered that it was important that the child is able to achieve some dry nights and so the method should only be used in children who are having some dry nights. The GDG also considered that the age of the child may be important when considering use of reward systems. While younger children may engage with these

methods it is possible that older children might not. The principles of recognising good behaviour however remains important for older children.

The GDG considered that healthcare professionals should ensure that they can give appropriate advice to parents and carers about the use of reward systems. The use of reward systems can involve considerable expertise and access to psychological support both for training of other professionals and for involvement with individual children may be important.

10.2.5 Recommendations

10.2.5.1 Explain to children and parents or carers that reward systems with positive rewards for agreed behaviour rather than dry nights should be used either alone or in conjunction with other treatments for bedwetting. For example, rewards may be given for :

- *drinking recommended levels of fluid during the day*
- *using the toilet to pass urine before sleep*
- *engaging in management (for example, taking medication or helping to change sheets).[1.7.1]*

10.2.5.2 Inform parents or carers that they should not use systems that penalise or remove previously gained rewards.[1.7.2]

10.2.5.3 Advise parents or carers to use reward systems alone for the initial treatment of bedwetting in young children who have some dry nights.[1.7.3]

11 Dry bed training for the management of bedwetting

11.1 Introduction

Dry bed training is a multi-component intervention for the management of nocturnal enuresis.

Dry bed training (DBT) was first described in Azrin (1974)⁴. The dry bed training procedure was described as a first night of intensive training which included positive practice one hour before bedtime, being given fluid at bed time, an alarm, hourly waking, and cleanliness training when the child was wet. After the initial nights treatment, post training supervision was given which continued to include an alarm, positive practice if the child was wet the night before, waking the child when parent went to bed, cleanliness training if the child wet the bed, and praise if the child was dry in the morning. If the child was dry for 7 consecutive dry nights the alarm was removed, and the parent would continue to check the bed in the morning. If the child was wet, cleanliness training would be used and positive practice was given the following evening. If the child was wet twice in a week, then post training supervision was started again.

Bollard (1981)¹⁵, Nawaz (2002)¹¹¹, Bennett (1985)¹¹, and Bollard (1982)¹⁷ used dry bed training as described in Azrin 1974⁴. However, some variations applied: Nawaz (2002)¹¹¹ specifically stated they included the trainer staying with the child on the first night. Bennett (1985)¹¹ adapted it to have the parents as the trainers. Bollard (1982)¹⁷ also included weekly meetings for parents and children. Keating (1983)⁸¹ used the method described in Azrin (1978)⁵ which was similar to the method in Azrin (1974)⁴, but also included star charts and rewards, training in the afternoon before the first night and hourly waking only until 1 am.

The comparisons included in the evidence review on the effectiveness of dry bed training are dry bed training with or without an alarm compared to no treatment; comparisons of different types of dry bed training with or without an alarm; dry bed training with or without an alarm compared to other treatments; dry bed training with or without an alarm compared to combination of treatments.

11.2 What is the clinical and cost effectiveness of dry bed training for children and young people under 19 years who have bedwetting?

11.2.1 Evidence review

11.2.1.1 Dry bed training (without an alarm) compared to no treatment

Table 11-1: Dry bed training without an alarm compared to no treatment - Clinical summary of findings

Outcome	DBT without alarm	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	7/30 (23.3%)	2/30 (6.7%)	RR 2.9 (0.75 to 11.14)	127 more per 1000 (from 17 fewer to 679 more)	VERY LOW
Mean number of wet nights per week at the end treatment (no sd)	30	30	-	not pooled	VERY LOW
Number of children who relapsed	2/5 (40%)	2/2 (100%)	RR 0.5 (0.17 to 1.46)	500 fewer per 1000 (from 830 fewer to 460 more)	VERY LOW

11.2.1.2 Dry bed training (without an alarm) compared to dry bed training with an alarm

Table 11-2: Dry bed training without an alarm compared to dry bed training with an alarm - Clinical summary of findings

Outcome	DBT without alarm	DBT with an alarm – therapist at home	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	7/30 (23.3%)	29/30 (96.7%)	RR 0.26 (0.14 to 0.48)	716 fewer per 1000 (from 503 fewer to 832 fewer)	LOW
Mean number of wet nights per week at the end of treatment (no sd)	30	30	-	not pooled	VERY LOW
Number of children who relapsed or failed	6/15 (40%)	8/30 (26.7%)	RR 1.45 (0.59 to 3.54)	120 more per 1000 (from 109 fewer to 678 more)	VERY LOW

Table 10-6: Dry bed training without an alarm compared to dry bed training with an alarm with therapist at hospital - Clinical summary of findings

Outcome	DBT without alarm	DBT with an alarm – therapist at hospital	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	5/20 (25%)	20/20 (100%)	RR 0.27 (0.13 to 0.55)	730 fewer per 1000 (from 450 fewer to 870 fewer)	LOW
Mean number of wet nights per week at the end of treatment (no sd)	20	20	-	not pooled	VERY LOW
Number of children who relapsed	2/5 (40%)	6/20 (30%)	RR 1.33 (0.38 to 4.72)	99 more per 1000 (from 186 fewer to 1000 more)	VERY LOW

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Table 11-3: Dry bed training without an alarm compared to dry bed training with an alarm with parent as therapist - Clinical summary of findings

Outcome	DBT without alarm	DBT with an alarm – parents as therapist	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	5/20 (25%)	20/20 (100%)	RR 0.27 (0.13 to 0.55)	730 fewer per 1000 (from 450 fewer to 870 fewer)	LOW
Mean number of wet nights per week at the end of treatment (no sd)	20	20	-	not pooled	VERY LOW
Number of children who relapsed	2/5 (40%)	4/20 (20%)	RR 2 (0.5 to 8)	200 more per 1000 (from 100 fewer to 1000 more)	VERY LOW

11.2.1.3 Dry bed training (without an alarm) compared to alarm

Table 11-4: Dry bed training without an alarm compared to an alarm - Clinical summary of findings

Outcome	DBT without alarm	Alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	5/20 (25%)	16/20 (80%)	RR 0.31 (0.14 to 0.69)	552 fewer per 1000 (from 248 fewer to 688 fewer)	LOW
Mean number of wet nights per week at the end treatment (no sd)	20	20	-	not pooled	VERY LOW
Number of children who relapsed	2/5 (40%)	6/16 (37.5%)	RR 1.07 (0.31 to 3.71)	26 more per 1000 (from 259 fewer to 1000 more)	VERY LOW

11.2.1.4 *Dry bed training with an alarm compared to no treatment*

Table11-5: Dry bed training with an alarm compared to no treatment - Clinical summary of findings

Outcome	DBT with an alarm	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	29/30 (96.7%)	2/30 (6.7%)	RR 9.34 (3.2 to 27.27)	559 more per 1000 (from 147 more to 1000 more)	LOW
Mean number of wet nights per week at the end of treatment (no sd)	30	30	-	not pooled	VERY LOW
Number of children who relapsed	5/20 (25%)	2/2 (100%)	RR 0.31 (0.13 to 0.76)	690 fewer per 1000 (from 240 fewer to 870 fewer)	VERY LOW

Table11-6: Dry bed training with an alarm with therapist at hospital compared to no treatment - Clinical summary of findings

Outcome	DBT with an alarm – therapist at hospital	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	20/20 (100%)	2/20 (10%)	RR 8.2 (2.56 to 26.3)	720 more per 1000 (from 156 more to 1000 more)	LOW
Mean number of wet nights per week at the end of treatment (no sd)	20	20	-	not pooled	VERY LOW
Number of children who relapsed	6/20 (30%)	2/2 (100%)	RR 0.37 (0.16 to 0.84)	630 fewer per 1000 (from 160 fewer to 840 fewer)	VERY LOW

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Table 11-7: Dry bed training with an alarm with parent as therapist compared to no treatment - Clinical summary of findings

Outcome	DBT with an alarm –parents as therapist	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	20/20 (100%)	2/20 (10%)	RR 8.2 (2.56 to 26.3)	720 more per 1000 (from 156 more to 1000 more)	LOW
Mean number of wet nights per week at the end of treatment (no sd)	20	20	-	not pooled	VERY LOW
Number of children who relapsed	4/20 (20%)	2/2 (100%)	RR 0.26 (0.1 to 0.67)	740 fewer per 1000 (from 330 fewer to 900 fewer)	LOW

11.2.1.5 Types of dry bed training with an alarm

Table 11-8: Dry bed training with an alarm with therapist at home compared to dry bed training with an alarm with therapist at hospital - Clinical summary of findings

Outcome	DBT with an alarm – therapist at home	DBT with an alarm – therapist at hospital	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	20/20 (100%)	20/20 (100%)	not pooled	not pooled	LOW
Mean number of wet nights per week at the end of treatment (no sd)	20	20	-	not pooled	VERY LOW

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Number of children who relapsed	5/20 (25%)	6/20 (30%)	RR 0.83 (0.3 to 2.29)	51 fewer per 1000 (from 210 fewer to 387 more)	VERY LOW
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Table 11-9: Dry bed training with an alarm with therapist at home compared to dry bed training with an alarm with parents as therapist - Clinical summary of findings

Outcome	DBT with an alarm – therapist at home	DBT with an alarm –parents as therapist	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	20/20 (100%)	20/20 (100%)	not pooled	not pooled	LOW
Mean number of wet nights per week at the end of treatment (no sd)	20	20	-	not pooled	VERY LOW
Number of children who relapsed	5/20 (25%)	4/20 (20%)	RR 1.25 (0.39 to 3.99)	50 more per 1000 (from 122 fewer to 598 more)	VERY LOW

Table 11-10: Dry bed training with an alarm with therapist at hospital compared to dry bed training with an alarm with parents as therapist - Clinical summary of findings

Outcome	DBT with an alarm – therapist at hospital	DBT with an alarm –parents as therapist	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	20/20 (100%)	20/20 (100%)	not pooled	not pooled	LOW
Mean number of wet nights per week at the end of treatment (no sd)	20	20	-	not pooled	VERY LOW

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Number of children who relapsed	6/20 (30%)	4/20 (20%)	RR 1.5 (0.5 to 4.52)	100 more per 1000 (from 100 fewer to 704 more)	VERY LOW
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11.2.1.6 *Dry bed training with an alarm compared to alarms*

Table 11-11: Dry bed training with an alarm compared to an alarm - Clinical summary of findings

Outcome	DBT with an alarm – therapist at home	Alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	25/30 (83.3%)	20/29 (69%)	RR 1.24 (0.99 to 1.55)	166 more per 1000 (from 7 fewer to 379 more)	VERY LOW
Mean number of wet nights at the end of treatment	10	9	-	MD 0.4 (-2.75 to 3.55)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	20	20	-	not pooled	VERY LOW
Number of children who dropped out	10/20 (50%)	9/18 (50%)	RR 1 (0.53 to 1.89)	0 fewer per 1000 (from 235 fewer to 445 more)	VERY LOW
Number of children who relapsed	5/20 (25%)	6/16 (37.5%)	RR 0.67 (0.25 to 1.79)	124 fewer per 1000 (from 281 fewer to 296 more)	VERY LOW

Table 11-12: Dry bed training with an alarm with therapist at hospital compared to an alarm - Clinical summary of findings

Outcome	DBT with an alarm – therapist at hospital	Alarm	Relative risk (95% CI)	Absolute effect	Quality
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NOCTURNAL ENURESIS: the management of bedwetting in children and young people – FINAL VERSION

Number of children who achieved 14 consecutive dry nights	20/20 (100%)	16/20 (80%)	RR 1.24 (0.98 to 1.57)	192 more per 1000 (from 16 fewer to 456 more)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	20	20	-	not pooled	VERY LOW
Number of children who relapsed	6/20 (30%)	6/16 (37.5%)	RR 0.8 (0.32 to 2.01)	75 fewer per 1000 (from 255 fewer to 379 more)	VERY LOW

Table 11-13: Dry bed training with an alarm with parents as therapist compared to an alarm - Clinical summary of findings

Outcome	DBT with an alarm – parents as therapist	Alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	20/20 (100%)	16/20 (80%)	RR 1.24 (0.98 to 1.57)	192 more per 1000 (from 16 fewer to 456 more)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	20	20	-	not pooled	VERY LOW
Number of children who relapsed	4/20 (20%)	6/16 (37.5%)	RR 0.53 (0.18 to 1.57)	176 fewer per 1000 (from 308 fewer to 214 more)	VERY LOW

11.2.1.7 *Dry bed training with an alarm compared to stop-start training*

Table 11-14: Dry bed training with an alarm compared to stop start training - Clinical summary of findings

Outcome	DBT with an alarm	Bladder training	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	5/10 (50%)	2/12 (16.7%)	RR 3 (0.73 to 12.27)	334 more per 1000 (from 45 fewer to 1000 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	10	12	-	MD -1.85 (-5.4 to 1.7)	VERY LOW
Number of children who dropped out	10/20 (50%)	11/23 (47.8%)	RR 1.05 (0.57 to 1.93)	24 more per 1000 (from 206 fewer to 445 more)	VERY LOW

11.2.1.8 *Dry bed training with an alarm compared to star charts*

Table 11-15: Dry bed training with an alarm compared to star charts - Clinical summary of findings

Outcome	DBT with an alarm	Star chart	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	5/10 (50%)	0/9 (0%)	RR 10 (0.63 to 158.87)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	10	9	-	MD -3.75 (-6.79 to -0.71)	VERY LOW
Number of children who dropped out	10/20 (50%)	3/12 (25%)	RR 2 (0.68 to 5.85)	250 more per 1000 (from 80 fewer to 1000 more)	VERY LOW

11.2.1.9 *Dry bed training (without an alarm) compared to no treatment for children with bedwetting wetting*

Table 11-16: Dry bed training without an alarm at hospital with parent and child compared to no treatment for children with bedwetting - Clinical summary of findings

Outcome	DBT without alarm – hospital parent and child	No treatment	Relative risk (95% CI)	Absolute effect	Quality
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NOCTURNAL ENURESIS: the management of bedwetting in children and young people – FINAL VERSION

Mean number of wet nights per week at the end of treatment (no sd)	7	7	-	not pooled	VERY LOW
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Table 11-17: Dry bed training without an alarm at home with parent and child compared to no treatment for children with bedwetting - Clinical summary of findings

Outcome	DBT without alarm – home parent and child	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment (no sd)	9	7	-	not pooled	VERY LOW

Table 11-18: Dry bed training without an alarm at hospital with parent compared to no treatment for children with bedwetting - Clinical summary of findings

Outcome	DBT without alarm – hospital parent	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment (no sd)	7	7	-	not pooled	VERY LOW

11.2.1.10 Dry bed training (without an alarm) compared to types to dry bed training for children with bedwetting

Table 11-19: Dry bed training without an alarm at hospital with parent and child compared to dry bed training without an alarm at home with parent and child for children with bedwetting - Clinical summary of findings

Outcome	DBT without alarm – hospital parent and child	DBT without alarm – home parent and child	Relative risk (95% CI)	Absolute effect	Quality
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NOCTURNAL ENURESIS: the management of bedwetting in children and young people – FINAL VERSION

Number of children who achieved 14 consecutive dry nights	7/7 (100%)	5/9 (55.6%)	RR 1.7 (0.95 to 3.07)	389 more per 1000 (from 28 fewer to 1000 more)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	7	9	-	not pooled	VERY LOW
Number of children who relapsed	2/7 (28.6%)	2/5 (40%)	RR 0.71 (0.15 to 3.5)	116 fewer per 1000 (from 340 fewer to 1000 more)	VERY LOW

Table 11-20: Dry bed training without an alarm at hospital with parent and child compared to dry bed training without an alarm at hospital with parent for children with bedwetting - Clinical summary of findings

Outcome	DBT without alarm – hospital parent and child	DBT without alarm – hospital parent	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	7/7 (100%)	6/7 (85.7%)	RR 1.15 (0.79 to 1.68)	129 more per 1000 (from 180 fewer to 583 more)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	7	7	-	not pooled	VERY LOW
Number of children who relapsed	2/7 (28.6%)	2/6 (33.3%)	RR 0.86 (0.17 to 4.37)	47 fewer per 1000 (from 276 fewer to 1000 more)	VERY LOW

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Table 11-21: Dry bed training without an alarm at home with parent and child compared to dry bed training without an alarm at hospital with parent and child for children with bedwetting - Clinical summary of findings

Outcome	DBT without alarm –home parent and child	DBT without alarm – hospital parent and child	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	5/9 (55.6%)	6/7 (85.7%)	RR 0.65 (0.34 to 1.25)	300 fewer per 1000 (from 566 fewer to 214 more)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	9	7	-	not pooled	VERY LOW
Number of children who relapsed	2/5 (40%)	2/6 (33.3%)	RR 1.2 (0.25 to 5.71)	67 more per 1000 (from 250 fewer to 1000 more)	VERY LOW

11.2.1.11 Dry bed training with an alarm compared to no treatment for children with bedwetting

Table 11-22: Dry bed training with an alarm compared to no treatment for children with bedwetting - Clinical summary of findings

Outcome	DBT with an alarm	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	8/12 (66.7%)	1/12 (8.3%)	RR 8 (1.17 to 54.5)	581 more per 1000 (from 14 more to 1000 more)	LOW
Mean number of dry nights per week at the end of treatment	12	12	-	MD -4.17 (-5.67 to -2.67)	MODERATE

11.2.1.12 Dry bed training with an alarm compared to alarms for children with bedwetting

Table 11-23 Dry bed training with an alarm compared to an alarm for children with bedwetting - Clinical summary of findings

Outcome	DBT with an alarm	Alarm	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	8/12 (66.7%)	3/12 (25%)	RR 2.67 (0.93 to 7.69)	418 more per 1000 (from 17 fewer to 1000 more)	LOW
Mean number of dry nights per week at the end of treatment	12	12	-	MD -2.42 (-4.13 to -0.71)	LOW
Number of children who relapsed	1/8 (12.5%)	1/3 (33.3%)	RR 0.38 (0.03 to 4.27)	206 fewer per 1000 (from 323 fewer to 1000 more)	LOW

11.2.2 Network Meta-Analysis

Dry bed training was amongst the interventions included in a network meta-analysis of interventions used for nocturnal enuresis. The summary of results of this analysis is presented in chapter 24 and a detailed description of the analysis is presented in appendix F. If studies did not meet the inclusion criteria of the network meta-analysis protocol as stated in appendix F they were not included in the network meta-analysis

11.2.3 Evidence statements

Studies include children with bedwetting and possible daytime symptoms

Dry bed training with an alarm versus dry bed training without an alarm

Bollard (1981)¹⁵, Bollard (1982)¹⁷

- Two studies showed children treated with dry bed training and an alarm were more likely to achieve 14 consecutive dry nights compared to children treated with dry bed training without an alarm. Relative risk 0.26, 95% CI 0.14, 0.48. Children in Bollard (1981)¹⁵ had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks; children in Bollard (1982)¹⁷ had a mean age of 8 years and 9 years and 4 months and had treatment for 8 weeks.
- Two studies showed children treated with dry bed training and an alarm had 3.2 to 3.8 fewer wet nights per week at the end of treatment compared to children treated with dry bed training without an alarm. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Children in Bollard (1981)¹⁵ had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks; children in Bollard (1982)¹⁷ had a mean age of 8 years and 9 years and 4 months and had treatment for 8 weeks.

Dry bed training without an alarm

Bollard (1981)¹⁵, Bollard (1982)¹⁷

- Two studies showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training (without an alarm) and children who had no treatment. Relative risk 2.9, 95% CI 0.75, 11.14. Children in Bollard (1981)¹⁵ had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks; children in Bollard (1982)¹⁷ had a mean age of 8 years and 9 years and 4 months and had treatment for 8 weeks.
- Two studies showed children treated with dry bed training (without an alarm) had 0.6 to 2.05 fewer wet nights per week at the end of treatment compared to children who had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children in Bollard (1981)¹⁵ had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks; children in Bollard (1982)¹⁷ had a mean age of 8 years and 9 years and 4 months and had treatment for 8 weeks.
- Two studies showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training without an alarm and children treated with dry bed training and an alarm. Relative risk 1.45, 95% CI 0.59, 3.54. Children in Bollard (1981)¹⁵ had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks; children in Bollard (1982)¹⁷ had a mean age of 8 years and 9 years and 4 months and had treatment for 8 weeks.

Bollard (1981)¹⁵

- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training (without an alarm) and children who had no treatment. Relative risk 0.5, 95% CI 0.17, 1.46. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children treated with dry bed training with an alarm with therapist at hospital were more likely to achieve 14 consecutive dry nights

compared to children treated with dry bed training without an alarm. Relative risk 0.27, 95% CI 0.13, 0.55. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.

- One study showed children treated with dry bed training and an alarm with therapist at hospital had 3.8 fewer wet nights per week at the end of treatment compared to children treated with dry bed training without an alarm. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training without an alarm and children treated with dry bed training and an alarm with therapist at hospital. Relative risk 1.33, 95% CI 0.38, 4.72. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children treated with dry bed training with an alarm with parents as the therapist were more likely to achieve 14 consecutive dry nights compared to children treated with dry bed training without an alarm. Relative risk 0.27, 95% CI 0.13, 0.55. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children treated with dry bed training and an alarm with parent as therapist had 3.8 fewer wet nights per week at the end of treatment compared to children treated with dry bed training without an alarm. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training without an alarm and children treated with dry bed training and an alarm with parent as therapist. Relative risk 2, 95% CI 0.5, 8. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children treated with an alarm were more likely to achieve 14 consecutive dry nights compared to children treated with dry bed training (without an alarm). Relative risk 0.31, 95% CI 0.14, 0.69. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.

- One study showed children treated with an alarm had 3.2 fewer wet nights per week at the end of treatment compared to children treated with dry bed training (without an alarm). No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training (without an alarm) and children treated with an alarm. Relative risk 1.07, 95% CI 0.31, 3.71. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.

Dry bed training with an alarm

Bollard (1981)¹⁵, Bollard (1982)¹⁷

- Two studies showed children treated with dry bed training and an alarm were more likely to achieve 14 consecutive dry nights compared to children who had no treatment. Relative risk 9.34, 95% CI 3.2, 27.27. Children in Bollard (1981)¹⁵ had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks; children in Bollard (1982)¹⁷ had a mean age of 8 years and 9 years and 4 months and had treatment for 8 weeks.
- Two studies showed children treated with dry bed training and an alarm had 4.4 to 5.1 fewer wet nights per week at the end of treatment compared to children who had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children in Bollard (1981)¹⁵ had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks; children in Bollard (1982)¹⁷ had a mean age of 8 years and 9 years and 4 months and had treatment for 8 weeks.

Bollard (1981)¹⁵

- One study showed children who had no treatment were more likely to relapse compared to children treated with dry bed training and an alarm. Relative risk 0.31, 95% CI 0.13, 0.76. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children treated with dry bed training and an alarm with the therapist at the hospital were more likely to achieve 14 consecutive dry

nights compared to children who had no treatment. Relative risk 8.2, 95% CI 2.56, 26.3. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.

- One study showed children treated with dry bed training and an alarm with the therapist at the hospital had 4.4 fewer wet nights per week at the end of treatment compared to children who had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children who had no treatment were more likely to relapse compared to children treated with dry bed training and an alarm with the therapist at the hospital. Relative risk 0.37, 95% CI 0.16, 0.84. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children treated with dry bed training and an alarm with the parents as the therapist were more likely to achieve 14 consecutive dry nights compared to children who had no treatment. Relative risk 8.2, 95% CI 2.56, 26.3. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children treated with dry bed training and an alarm with parents as the therapist had 4.4 fewer wet nights per week at the end of treatment compared to children who had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children who had no treatment were more likely to relapse compared to children treated with dry bed training and an alarm with the parents as the therapist. Relative risk 0.26, 95% CI 0.1, 0.67. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training with an alarm with the therapist at home and children treated with dry bed training with an alarm and the therapist at hospital. Both groups had 20 out of 20 achieving 14 consecutive dry nights. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.

- One study showed there was no difference in the number of wet nights per week at the end of treatment between children treated with dry bed training with an alarm with the therapist at home and children treated with dry bed training with an alarm and the therapist at hospital. Both groups had 0 wet nights. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training with an alarm with the therapist at home and children treated with dry bed training with an alarm and the parents as the therapist. Both groups had 20 out of 20 achieving 14 consecutive dry nights. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no difference in the number of wet nights per week at the end of treatment between children treated with dry bed training with an alarm with the therapist at home and children treated with dry bed training with an alarm and the parents as the therapist. Both groups had 0 wet nights. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training with an alarm with the therapist at home and children treated with dry bed training with an alarm and the parents as the therapist. Relative risk 1.25, 95% CI 0.39, 3.99. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training with an alarm with the therapist at hospital and children treated with dry bed training with an alarm and the parents as the therapist. Both groups had 20 out of 20 achieving 14 consecutive dry nights. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no difference in the number of wet nights per week at the end of treatment between children treated with dry bed training with an alarm with the therapist at hospital and children treated with dry bed

training with an alarm and the parents as the therapist. Both groups had 0 wet nights. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.

- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training with an alarm with the therapist at hospital and children treated with dry bed training with an alarm and the parents as the therapist. Relative risk 1.5, 95% CI 0.5, 4.52. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children treated with dry bed training and an alarm had 0.6 fewer wet nights per week at the end of treatment compared to children treated with an alarm. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children in had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training and an alarm with the therapist at hospital and children treated with an alarm. Relative risk 1.24, 95% CI 0.98, 1.57. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed children treated with dry bed training and an alarm with the therapist at hospital had 0.6 fewer wet nights per week at the end of treatment compared to children treated with an alarm. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training and an alarm with the therapist at hospital and children treated with an alarm. Relative risk 0.8, 95% CI 0.32, 2.01. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training and an alarm with the parents as the therapist

and children treated with an alarm. Relative risk 1.24, 95% CI 0.98, 1.57. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.

- One study showed children treated with dry bed training and an alarm with the parents as the therapist had 0.6 fewer wet nights per week at the end of treatment compared to children treated with an alarm. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training and an alarm with the parents as the therapist and children treated with an alarm. Relative risk 0.53, 95% CI 0.18, 1.57. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training and an alarm and children treated with an alarm. Relative risk 0.67, 95% CI 0.25, 1.79. Children had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.

Bennett (1985) ¹¹

- One study showed there was no statistically significant difference in the mean number of wet nights per week at the end of treatment between children treated with dry bed training and an alarm and children treated with an alarm. Mean difference 0.4, 95% CI -2.75, 3.55. Children had a mean age of 8.5 years and had treatment for 12 weeks.
- One study showed there was no difference in the number of children who dropped out between children treated with dry bed training and an alarm and children treated with an alarm. Relative risk 1, 95% CI 0.53, 1.89. Children in had a mean age of 8.5 years and had treatment for 12 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training and an alarm and children treated with stop-start training. Relative risk 3, 95% CI 0.73, 12.27. Children had a mean age of 8.5 years and had treatment for 12 weeks.

- One study showed children treated with dry bed training and an alarm had fewer wet nights per week at the end of treatment compared to children treated with stop-start training. Mean difference -1.85, 95% CI -5.4, 1.7. Children had a mean age of 8.5 years and had treatment for 12 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with dry bed training and an alarm and children treated with stop-start training. Relative risk 1.05, 95% CI 0.57, 1.93. Children had a mean age of 8.5 years and had treatment for 12 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training and an alarm and children treated with star charts. Relative risk 10, 95% CI 0.63, 158.87. Children had a mean age of 8.5 years and had treatment for 12 weeks.
- One study showed children treated with dry bed training and an alarm had fewer wet nights per week at the end of treatment compared to children treated with star charts. Mean difference -3.75, 95% CI -6.79, -0.71. Children had a mean age of 8.5 years and had treatment for 12 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with dry bed training and an alarm and children treated with star charts. Relative risk 2, 95% CI 0.68, 5.85. Children had a mean age of 8.5 years and had treatment for 12 weeks.

Bennett (1985)¹¹, Bollard (1981)¹⁵

- Two studies showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training and an alarm and children treated with an alarm. Relative risk 1.24, 95% CI 0.99, 1.55. Children in Bennett (1985)¹¹ had a mean age of 8.5 years and had treatment for 12 weeks; children in Bollard (1981)¹⁵ had a mean age of 8.1 and 9.3 years and had treatment for 20 weeks.

Studies include children with bedwetting only

Dry bed training without an alarm

Keating (1983)⁸¹

- One study showed children who had no treatment had 0.7 fewer wet nights per week at the end of treatment compared to children treated with dry bed training (without an alarm) with training at hospital for parent and child. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 years and had treatment for 5 weeks.
- One study showed children who had no treatment had 0.5 fewer wet nights per week at the end of treatment compared to children treated with dry bed training (without an alarm) with training at home for parent and child. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 years and had treatment for 5 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training (without an alarm) with training at hospital for parent and child and children treated with dry bed training (without an alarm) with training at home for parent and child. Relative risk 1.7, 95% CI 0.95, 3.07. Children had a mean age of 8.1 years and had treatment for 5 weeks.
- One study showed children treated with dry bed training (without an alarm) with training at home for parent and child had 0.2 fewer wet nights per week at the end of treatment compared to children treated with dry bed training (without an alarm) with training at hospital for parent and child. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 years and had treatment for 5 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training (without an alarm) with training at hospital for parent and child and children treated with dry bed training (without an alarm) with training at home for parent and child. Relative risk 0.71, 95% CI 0.15, 3.5. Children had a mean age of 8.1 years and had treatment for 5 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children

treated with dry bed training (without an alarm) with training at hospital for parent and child and children treated with dry bed training (without an alarm) with training at hospital for parent only. Relative risk 1.15, 95% CI 0.79, 1.68. Children had a mean age of 8.1 years and had treatment for 5 weeks.

- One study showed children treated with dry bed training (without an alarm) with training at hospital for parent only had 0.8 fewer wet nights per week at the end of treatment compared to children treated with dry bed training (without an alarm) with training at hospital for parent and child. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 years and had treatment for 5 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training (without an alarm) with training at hospital for parent and child and children treated with dry bed training (without an alarm) with training at hospital for parent only. Relative risk 0.86, 95% CI 0.17, 4.37. Children had a mean age of 8.1 years and had treatment for 5 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training (without an alarm) with training at home for parent and child and children treated with dry bed training (without an alarm) with training at hospital for parent only. Relative risk 0.65, 95% CI 0.34, 1.25. Children had a mean age of 8.1 years and had treatment for 5 weeks.
- One study showed children treated with dry bed training (without an alarm) with training at hospital for parent only had 0.6 fewer wet nights per week at the end of treatment compared to children treated with dry bed training (without an alarm) with training at home for parent and child. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 years and had treatment for 5 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training (without an alarm) with training at home for parent and child and

children treated with dry bed training (without an alarm) with training at hospital for parent only. Relative risk 1.2, 95% CI 0.25, 5.71. Children had a mean age of 8.1 years and had treatment for 5 weeks.

- One study showed children treated with dry bed training (without an alarm) with training at hospital for parent only had 0.1 fewer wet nights per week at the end of treatment compared to children who had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.1 years and had treatment for 5 weeks.

Dry bed training with an alarm

Nawaz (2002) ¹¹¹

- One study showed children treated with dry bed training and an alarm were more likely to achieve 14 consecutive dry nights compared to children who had no treatment. Relative risk 8, 95% CI 1.17, 54.5. Children had a mean age of 9.93 years and had treatment for 16 weeks.
- One study showed children treated with dry bed training and an alarm had fewer wet nights per week at the end of treatment compared to children who had no treatment. Mean difference -4.17, 95% CI -5.67 to -2.67. Children had a mean age of 9.93 years and had treatment for 16 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with dry bed training and an alarm and children treated with an alarm. Relative risk 2.67, 95% CI 0.93, 7.69. Children had a mean age of 9.93 years and had treatment for 16 weeks.
- One study showed children treated with dry bed training and an alarm had fewer wet nights per week at the end of treatment compared to children treated with an alarm. Mean difference -2.42, 95% CI -4.13 to -0.71. Children had a mean age of 9.93 years and had treatment for 16 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed between children treated with dry bed training and an alarm and children treated with an alarm. Relative risk 0.38,

95% CI 0.03, 4.27. Children had a mean age of 9.93 years and had treatment for 16 weeks.

NCGC network meta-analysis (see appendix F)

For children with bedwetting and possible daytime symptoms

- **The NCGC NMA showed there was no statistically significant difference in the number of children who achieved a full response between children treated with dry bed training without alarm and no treatment / placebo. Relative risk 2.497, 95% CI 0.754, 5.528. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**
- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with dry bed training with alarm and no treatment / placebo. Relative risk 8.919, 95% CI 7.736, 9.319. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**

For children with bedwetting only

- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with dry bed training with alarm and no treatment / placebo. Relative risk 8.116, 95% CI 2.538, 9.523. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**

For estimates of treatment effect relative to other active comparators, please see section 24.4 in chapter 24.

11.2.4 Evidence to recommendations

Relative values of different outcomes:

The review identified important relevant outcomes both in achieving dryness and in relapse: number of children who achieved 14 consecutive dry nights, mean number of wet nights per week at the end of treatment and the number of children who relapsed.

Trade off between clinical benefits and harms:

No evidence was found on the harms of dry bed training or the comparators the evidence considered. However the GDG highlighted the punitive elements of dry bed training and amount of effort and disruption caused by the programme.

Economic considerations:

No economic evidence was identified. GDG experience with dry bed training was limited, but they understood it to involve much more intensive follow-up, including multiple phone calls each week. Based on this, and the fact that dry bed training with or without an alarm was not shown to be more effective than treatment with an alarm alone, the GDG concluded that the incremental benefit is very unlikely to be justified by the increased cost relative to alarm alone.

Quality of evidence:

The clinical evidence identified was of small RCTs which gave wide confidence intervals in the outcomes of interest. The quality was low or very low for all outcomes.

Other considerations:

The evidence indicated that DBT without an alarm is unlikely to be any more effective than no treatment. However the data was of very limited methodological quality and neither study which examined this comparison was adequately powered to show a difference.

The evidence showed that when comparing DBT without an alarm to DBT with an alarm for 14 consecutive dry nights, DBT with an alarm was better than DBT without an alarm. This was statistically significant and the associated confidence interval was narrow.

The GDG considered the comparison of DBT with an alarm to an alarm alone an important comparison. In the population of children with bedwetting and possible daytime symptoms, both studies had a small sample size. The associated confidence interval was narrow, with no statistically significant difference between DBT and an alarm and alarm alone. In the study of children with bedwetting Nawaz (2002)¹¹¹ showed that there was no statistically significant difference in children having 14 consecutive dry nights, but did show that children treated with dry bed training and an alarm were statistically dryer than children treated with an alarm alone. The GDG considered the evidence is insufficient to consider DBT with an alarm over an alarm due to wide confidence intervals and the magnitude of effort required for possible improvement in one outcome of interest..

The GDG considered that some components of DBT as described by Azrin (1974)⁴ were unacceptably punitive, inappropriate and potentially psychologically damaging. The punitive elements were identified as: repetitive (20 times) positive practice, being told they were wet and informing visitors to the house they were trying to become dry, sleep loss even when dry (being woken to check if they were dry), and reprimanding as listed in Azrin (1974)⁴. The GDG considered that some aspects of ‘positive practice’ are part of using an alarm e.g. described in the study as a good practice if the alarm goes off and the child gets up and goes to the toilet. There is insufficient evidence that this should be practised so many times as described in Azrin (1974)⁴. The GDG supported praising the child for a dry night and for older children it was felt they should be involved with helping to clean (changing bedding and night clothes) the bed if there was a wet night. However as all dry bed training programmes included punitive elements it could not be recommended.

11.2.5 Recommendations

11.2.5.1 Do not use dry-bed training⁹ with or without an alarm for the treatment of bedwetting in children [1.14.2].

⁹ A training programme that combines a number of different behavioural interventions that may include rewards, punishment training routines and waking routines and may be undertaken with or without an enuresis alarm.

12 Enuresis Alarms in the management of bedwetting

12.1 Introduction

An enuresis alarm is a device that is activated by getting wet. According to Mowrer (1938)¹⁰⁷, the first enuresis alarms were bed-based, with the child sleeping on a pad or mat containing an electrical circuit. A bell would then ring as a result of the urine contacting the electrical circuit. There are several types of enuresis alarms available: pad-and-bell alarms where the sensor pad is positioned under a draw sheet beneath the child in the bed; body-worn alarms where the tiny sensor is attached to the child's pants e.g. between 2 pairs of tightly fitting underpants and the alarm is worn on the pyjama top; and vibrating alarms.

Alarms achieve dryness over time by training the child to recognise the need to pass urine and to wake to go to the toilet or hold on. As such it would be expected that they would be most successful in children with arousal difficulties rather than children who are overproducing urine at night. Where possible therefore the evidence review highlights the population of children included in the study i.e. bedwetting with daytime symptoms, bedwetting only and mono-symptomatic nocturnal enuresis (see 2.1.4 and 2.2 for more detail).

Alarms were compared in the evidence review to pharmacological interventions singly and to each in combination with alarm: desmopressin (spray, tablets and melts), imipramine, amitriptyline, nortriptyline, oxybutinin, , long-acting tolterodine. Alarms were also compared to dry bed training with enuresis alarm, retention control training and star charts.

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

12.2.1 Evidence review

Study populations- children with bedwetting and possible daytime symptoms

12.2.1.1 Enuresis alarm compared to no treatment for children with bedwetting and possible daytime symptoms

Six randomised control trials evaluated enuresis alarm treatment compared to no treatment, a waiting list group; these were: **Baker (1969)**⁷, **Bollard (1981)**¹⁵, **Bollard (1982)**¹⁶, **Houts (1986)**⁷³, **Jehu (1977)**⁷⁵ and **Moffatt (1987)**¹⁰³

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Table 12-1: Enuresis alarm compared to no treatment - Clinical summary of findings

Outcome	Alarm	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	108/141 (76.6%)	3/135 (2.2%)	RR 16.9 (7.17 to 39.85)	350 more per 1000 (from 136 more to 855 more)	LOW
Mean number of wet nights per week at end of treatment (no SDs)	14	11	-	not pooled	VERY LOW
Number of drop outs at end of trial	4/34 (11.8%)	0/31 (0%)	RR 4.16 (0.5 to 34.6)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

12.2.1.2 *Unsupervised enuresis alarm compared to supervised enuresis alarm for children with bedwetting and possible daytime symptoms*

One randomised control trial **Bollard (1981)**¹⁵ compared the supervision of enuresis alarm treatment for children with nocturnal enuresis, comparing an unsupervised enuresis alarm to a supervised enuresis alarm. The supervision was the parent or child (if old enough) contacting the author by telephone to report progress at a specific time, if contact was not made the author contacted the parent or child by telephone or letter.

Table 12-2 Unsupervised enuresis alarm compared to supervised enuresis alarm - Clinical summary of findings

Outcome	Unsupervised alarm	Supervised alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	12/15 (80%)	9/15 (60%)	RR 1.33 (0.82 to 2.16)	198 more per 1000 (from 108 fewer to 696 more)	VERY LOW
Mean number of wet nights per week at end of treatment (no SDs)	15	15	-	not pooled	VERY LOW

12.2.1.3 Enuresis alarm compared to imipramine

Two randomised control trials **Fournier (1987)**⁶⁰ and **Kolvin (1972)**⁸³ compared enuresis alarm to imipramine,. **Fournier (1987)**⁶⁰ gave 25 mg imipramine to children, **Kolvin (1972)**⁸³ did not state the dose of imipramine given to children.

Table 12-3: Enuresis alarm compared to imipramine - Clinical summary of findings

Outcome	Alarm	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Over 80% improvement in number of wet nights at the end of treatment	17/32 (53.1%)	16/35 (45.7%)	RR 1.16 (0.71 to 1.89)	73 more per 1000 (from 133 fewer to 407 more)	VERY LOW
Mean number of wet nights per week at end of treatment (no SDs)	40	43	-	not pooled	VERY LOW
Mean number of wet nights per week at follow-up (no SDs)	32	30	-	not pooled	LOW

12.2.1.4 Enuresis alarm compared to amitriptyline

One randomised control trial **Danquah (1975)**³⁸ compared enuresis alarm to amitriptyline.

Table 12- 4 Increasing desmopressin compared to placebo - Clinical summary of findings

Outcome	Desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week after treatment (no SDs)	10	10	-	not pooled	VERY LOW

12.2.1.5 Enuresis alarm compared to enuresis alarm with intranasal desmopressin

One randomised controlled trial **Bradbury (1995)**¹⁸ compared enuresis alarms to enuresis alarms with intranasal desmopressin.

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Table 12-5: Enuresis alarm compared to enuresis alarm with desmopressin - Clinical summary of findings

Outcome	Alarm	Alarm and desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 4 consecutive dry weeks	16/27 (59.3%)	27/33 (81.8%)	RR 0.72 (0.51 to 1.03)	229 fewer per 1000 (from 401 fewer to 25 more)	LOW
Mean number of wet nights per week at end of treatment (no SDs)	35	36	-	not pooled	LOW
Number of children relapsed at 6 months	3/16 (18.8%)	4/27 (14.8%)	RR 1.27 (0.32 to 4.95)	40 more per 1000 (from 101 fewer to 585 more)	LOW
Number of drop outs at end of trial	2/35 (5.7%)	0/36 (0%)	RR 5.14 (0.26 to 103.37)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

12.2.1.6 Enuresis alarm and placebo compared to enuresis alarm with desmopressin

One randomised controlled trial **Sukhai (1989)**¹⁴⁴ compared enuresis alarms and placebo to enuresis alarms with desmopressin.

Table 12-6: Enuresis alarm and placebo compared to enuresis alarm and desmopressin - Clinical summary of findings

Outcome	Alarm and placebo	Alarm and desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment	28	28	-	MD 1 (0.79 to 1.21)	MODERATE

12.2.1.7 Enuresis alarm compared to enuresis alarm with imipramine

One randomised control trial **Fournier (1987)**⁶⁰, compared enuresis alarm alone to enuresis alarm with imipramine.

Table 12-7: Enuresis alarm compared to enuresis alarm and imipramine - Clinical summary of findings

Outcome	Alarm	Alarm and imipramine	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at follow-up	8	8	-	not pooled	VERY LOW

12.2.1.8 Enuresis alarm compared to dry bed training with an enuresis alarm

One randomised controlled trial, **Bennett (1985)**¹¹ compared enuresis alarm treatment to dry bed training which included the use of an enuresis alarm. **Bennett (1985)**¹¹ reported dry bed training to include waking schedule, retention control training, positive practice and cleanliness training.

Table 12-8: Enuresis alarm compared to dry bed training - Clinical summary of findings

Outcome	Alarm	DBT	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	4/9 (44.4%)	5/10 (50%)	RR 0.89 (0.34 to 2.32)	55 fewer per 1000 (from 330 fewer to 660 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	9	10	-	MD -0.4 (-2.09 to 1.29)	VERY LOW
Number of children who dropped out	9/18 (50%)	10/20 (50%)	RR 1 (0.53 to 1.89)	0 fewer per 1000 (from 235 fewer to 445 more)	VERY LOW

12.2.1.9 Enuresis alarm compared to retention control training with an enuresis alarm

Three randomised control trials **Fielding (1980)**⁵⁶, **Geffken (1986)**⁶² and **Houts (1986)**⁷³ compared enuresis alarm treatment to retention control treatment with an enuresis alarm.

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Table 12-9: Enuresis alarm compared to enuresis alarm and retention control training - Clinical summary of findings

Outcome	Alarm	Alarm and retention control training	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	31/43 (72.1%)	37/43 (86%)	RR 0.84 (0.68 to 1.04)	138 fewer per 1000 (from 275 fewer to 34 more)	VERY LOW
Mean change of number of wet nights during treatment (no SDs)	20	20	-	not pooled	VERY LOW
Mean change of number of wet nights during follow up (no SDs)	20	20	-	not pooled	VERY LOW
Number of children who relapsed at 6 months	5/12 (41.7%)	9/19 (47.4%)	RR 0.92 (0.42 to 2.02)	38 fewer per 1000 (from 275 fewer to 483 more)	VERY LOW
Number of children who relapsed at 12 months	5/12 (41.7%)	10/19 (52.6%)	RR 0.82 (0.38 to 1.77)	95 fewer per 1000 (from 326 fewer to 405 more)	VERY LOW
Number of drop outs by end of trial	3/15 (20%)	2/15 (13.3%)	RR 1.5 (0.29 to 7.73)	67 more per 1000 (from 94 fewer to 895 more)	VERY LOW

12.2.1.10 Enuresis alarm compared to enuresis alarm plus a star chart

Van Londen (1993)¹⁵⁶, a randomised controlled trial evaluated enuresis alarms compared to two types of star charts in combination with enuresis alarm treatment.

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Table 12-10: Enuresis alarm compared to enuresis alarm and star charts for correct behaviour - Clinical summary of findings

Outcome	Alarm	Alarm and star chart for correct behaviour	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 dry consecutive nights	26/36 (72.2%)	37/38 (97.4%)	RR 0.74 (0.6 to 0.91)	253 fewer per 1000 (from 88 fewer to 390 fewer)	VERY LOW
Number of relapses at 2.5 years	13/26 (50%)	10/37 (27%)	RR 1.85 (0.96 to 3.56)	230 more per 1000 (from 11 fewer to 691 more)	VERY LOW

Table 12 -11: Enuresis alarm compared to enuresis alarm and star charts for dry night - Clinical summary of findings

Outcome	Alarm	Alarm and star chart for dry night	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 dry consecutive nights	26/36 (72.2%)	33/39 (84.6%)	RR 0.85 (0.67 to 1.09)	127 fewer per 1000 (from 279 fewer to 76 more)	VERY LOW
Number of relapses at 2.5 years	13/26 (50%)	15/33 (45.5%)	RR 1.1 (0.64 to 1.88)	46 more per 1000 (from 164 fewer to 400 more)	VERY LOW

Table 12-12: Enuresis alarm and star chart for correct behaviour compared to enuresis alarm and star charts for dry night - Clinical summary of findings

Outcome	Alarm and star chart for correct behaviour	Alarm and star chart for dry night	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 dry consecutive nights	33/39 (84.6%)	37/38 (97.4%)	RR 0.87 (0.75 to 1)	127 fewer per 1000 (from 244 fewer to 0 more)	LOW

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Number of relapses at 2.5 years	15/33 (45.5%)	10/37 (27%)	RR 1.68 (0.88 to 3.22)	184 more per 1000 (from 32 fewer to 599 more)	VERY LOW
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Study populations- children with bedwetting only

12.2.1.11 Enuresis alarm compared to no treatment for children with bedwetting only

Four randomised control trials evaluated enuresis alarm treatment compared to no treatment, a waiting list group; **Lynch (1984)**⁹⁵, **Nawaz (2002)**¹¹¹, **Wagner (1982)**¹⁶⁰ and **Wagner (1985)**¹⁶² for children with bedwetting.

Table 12-13: Enuresis alarm compared to no treatment for children with bedwetting - Clinical summary of findings

Outcome	Alarm	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	28/55 (50.9%)	3/55 (5.5%)	RR 7.35 (2.56 to 21.11)	349 more per 1000 (from 86 more to 1000 more)	LOW
Mean number of wet nights per week at end of treatment	30	30	-	MD -2.78 (-4.42 to -1.14)	VERY LOW
Number of children who relapsed at 6 months	7/18 (38.9%)	2/2 (100%)	RR 0.54 (0.24 to 1.19)	460 fewer per 1000 (from 760 fewer to 190 more)	VERY LOW
Number of drop outs at end of trial	2/20 (10%)	2/20 (10%)	RR 1 (0.16 to 6.42)	0 fewer per 1000 (from 84 fewer to 542 more)	VERY LOW

12.2.1.12 Pad and bell enuresis alarm compared to body worn enuresis alarm for children with bedwetting only

One randomised control trial **Butler (1990)**²⁶, compared effectiveness of two different enuresis alarms, one body worn enuresis alarm and a pad and bell enuresis alarm for children with bedwetting.

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Table 12- 14: Pad and bell enuresis alarm compared to body worn enuresis alarm - Clinical summary of findings

Outcome	Pad and bell alarm	Body worn alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	14/20 (70%)	14/20 (70%)	RR 1 (0.67 to 1.5)	0 fewer per 1000 (from 231 fewer to 350 more)	MODERATE
Mean number of wet nights per week at end of treatment (no SDs)	17	18	-	not pooled	MODERATE
Number of children who relapsed at 6 months	4/14 (28.6%)	3/14 (21.4%)	RR 1.33 (0.36 to 4.9)	71 more per 1000 (from 137 fewer to 835 more)	MODERATE
Number of drop outs at end of trial	3/20 (15%)	2/20 (10%)	RR 1.5 (0.28 to 8.04)	50 more per 1000 (from 72 fewer to 704 more)	MODERATE

12.2.1.13 Enuresis alarm compared to desmopressin for children with bedwetting only

Two randomised control trials **Ng (2005)**¹¹⁵ and **Wille (1986)**¹⁶⁷ compared enuresis enuresis alarms to any form of desmopressin in children with bedwetting.

Table 12-15: Enuresis alarm compared to desmopressin - Clinical summary of findings

Outcome	Alarm	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	8/35 (22.9%)	16/38 (42.1%)	RR 0.54 (0.27 to 1.11)	194 fewer per 1000 (from 307 fewer to 46 more)	LOW
Number of children who achieved 5 wet nights in 28 nights	19/22 (86.4%)	17/24 (70.8%)	RR 1.22 (0.9 to 1.66)	156 more per 1000 (from 71 fewer to 467 more)	VERY LOW

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Mean number of wet nights per week at end of treatment	50	60	-	MD -0.46 (-1.53 to 0.62)	VERY LOW
Number of children who relapsed at 3 months	1/27 (3.7%)	19/33 (57.6%)	RR 0.09 (0.02 to 0.45)	524 fewer per 1000 (from 317 fewer to 564 fewer)	LOW
Number of children who dropped out by the end of the trial	8/57 (14%)	2/62 (3.2%)	RR 3.69 (0.95 to 14.34)	86 more per 1000 (from 2 fewer to 427 more)	VERY LOW
Adverse event - False alarm	21/22 (95.5%)	0/0 (0%)	not pooled	not pooled	LOW

12.2.1.14 Enuresis alarm compared to imipramine for children with bedwetting only

One randomised controlled trial **Wagner (1982)**¹⁶⁰ compared enuresis alarm to imipramine (25 mg for children < 32 kg, 50 mg for children > 32k g) for children with bedwetting and was identified.

Table 12-16: Enuresis alarm compared to imipramine for children with bedwetting - Clinical summary of findings

Outcome	Alarm	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	10/12 (83.3%)	4/12 (33.3%)	RR 2.5 (1.08 to 5.79)	500 more per 1000 (from 27 more to 1000 more)	VERY LOW
Mean number of wet nights per week at end of treatment (no SDs)	12	12	-	not pooled	VERY LOW
Number of children who relapsed at 6 months	5/10 (50%)	4/4 (100%)	RR 0.56 (0.29 to 1.07)	440 fewer per 1000 (from 710 fewer to 70 more)	VERY LOW

12.2.1.15 Enuresis alarm compared to enuresis alarm with desmopressin for children with bedwetting only

One randomised controlled trial **Ng (2005)**¹¹⁵ compared enuresis alarms to enuresis alarms with desmopressin for children bedwetting only

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Table 12-17: Enuresis alarm compared to enuresis alarm and desmopressin for children with bedwetting- Clinical summary of findings

Outcome	Alarm	Alarm and desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	8/35 (22.9%)	20/32 (62.5%)	RR 0.37 (0.19 to 0.71)	394 fewer per 1000 (from 181 fewer to 506 fewer)	MODERATE
Mean number of wet nights per week at the end of treatment	28	29	-	MD 1.5 (0.43 to 2.57)	LOW
Number of children who relapsed at 3 months	0/8 (0%)	7/20 (35%)	RR 0.16 (0.01 to 2.44)	294 fewer per 1000 (from 346 fewer to 504 more)	LOW
Number of children who dropped out by the end of the trial	7/35 (20%)	3/32 (9.4%)	RR 2.13 (0.6 to 7.56)	106 more per 1000 (from 38 fewer to 617 more)	LOW

12.2.1.16 Enuresis alarm compared to dry bed training with an enuresis alarm for children with bedwetting

One randomised controlled trial **Nawaz (2002)**¹¹¹ compared enuresis alarm treatment to dry bed training which included the use of an enuresis alarm for children with bedwetting. **Nawaz (2002)**¹¹¹ reported dry bed training to include waking schedule, retention control training, positive practice and cleanliness training.

Table 12-18: Enuresis alarm compared to dry bed training for children with bedwetting - Clinical summary of findings

Outcome	Alarm	DBT	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	3/12 (25%)	8/12 (66.7%)	RR 0.38 (0.13 to 1.08)	414 fewer per 1000 (from 580 fewer to 53 more)	LOW
Mean number of wet nights per week at the end of treatment	12	12	-	MD 2.42 (0.71 to 4.13)	LOW

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Number of children who relapsed at 6 months	1/3 (33.3%)	1/8 (12.5%)	RR 2.67 (0.23 to 30.4)	209 more per 1000 (from 96 fewer to 1000 more)	LOW
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12.2.1.17 Enuresis alarm compared to retention control training with an enuresis alarm for children with bedwetting

One randomised control trial **Fielding (1980)**⁵⁶ compared enuresis alarm treatment to retention control treatment which included an enuresis alarm for children with bedwetting.

Table 12-19: Enuresis alarm compared to enuresis alarm and retention control training for children with bedwetting - Clinical summary of findings

Outcome	Alarm	Alarm and retention control training	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	14/17 (82.4%)	11/16 (68.8%)	RR 1.2 (0.81 to 1.78)	138 more per 1000 (from 131 fewer to 537 more)	VERY LOW
Number of children who relapsed at 6 months	5/14 (35.7%)	3/11 (27.3%)	RR 1.31 (0.4 to 4.32)	85 more per 1000 (from 164 fewer to 906 more)	VERY LOW
Number of children who relapsed at 12 months	8/14 (57.1%)	4/11 (36.4%)	RR 1.57 (0.64 to 3.88)	207 more per 1000 (from 131 fewer to 1000 more)	VERY LOW

Study population- children with mono-symptomatic NE

12.2.1.18 Enuresis alarm compared to desmopressin for children with monosymptomatic nocturnal enuresis

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Two randomised control trials **Longstaffe (2000)**⁹² and **Tuygun (2007)**¹⁵¹ compared enuresis alarms to desmopressin, **Tuygun (2007)**¹⁵¹. Both studies considered children with monosymptomatic nocturnal enuresis.

Table 12-20: Enuresis alarm compared to desmopressin for children with monosymptomatic nocturnal enuresis - Clinical summary of findings

Outcome	Alarm	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive or a 90% improvement in the number of dry nights	55/96 (57.3%)	54/109 (49.5%)	RR 1.16 (0.89 to 1.5)	79 more per 1000 (from 54 fewer to 248 more)	VERY LOW
50%-90% reduction in number of wet nights at end of treatment	9/35 (25.7%)	15/49 (30.6%)	RR 0.84 (0.42 to 1.7)	49 fewer per 1000 (from 177 fewer to 214 more)	VERY LOW
Mean number of wet nights per month at end of treatment	35	49	-	MD -7.29 (-11.27 to -3.31)	VERY LOW
Number of children relapsed at 6 months	10/35 (28.6%)	27/49 (55.1%)	RR 0.52 (0.29 to 0.93)	264 fewer per 1000 (from 39 fewer to 391 fewer)	VERY LOW
Number of children who dropped out of the trial	8/61 (13.1%)	5/60 (8.3%)	RR 1.57 (0.55 to 4.54)	47 more per 1000 (from 37 fewer to 294 more)	LOW

12.2.1.19 *Enuresis alarm compared to enuresis alarm with desmopressin for children with monosymptomatic nocturnal enuresis*

One randomised controlled trial **Ozden (2008)**¹¹⁷ compared enuresis alarms to enuresis alarms with desmopressin for children with monosymptomatic nocturnal enuresis and was identified in the update search.

Table 12- 21: Enuresis alarm compared to enuresis alarm with desmopressin for children with monosymptomatic nocturnal enuresis - Clinical summary of findings

Outcome	Alarm	Alarm and desmopressin	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved at least 75% reduction in the number of wet nights	7/22 (31.8%)	6/30 (20%)	RR 1.59 (0.62 to 4.08)	118 more per 1000 (from 76 fewer to 616 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	22	30	-	MD 0.5 (0.19 to 0.81)	VERY LOW
Number of children who dropped out by the end of the trial	5/22 (22.7%)	3/30 (10%)	RR 2.27 (0.61 to 8.52)	127 more per 1000 (from 39 fewer to 752 more)	VERY LOW

Study populations- children with severe wetting

12.2.1.20 Enuresis alarm compared to no treatment for children with severe wetting

One randomised controlled trial **Ronen (1992)**¹³¹ compared enuresis alarms to no treatment for children with severe wetting.

Table 12-22: Enuresis alarm compared to no treatment for children with severe wetting - Clinical summary of findings

Outcome	Alarm	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	12/19 (63.2%)	0/18 (0%)	RR 23.75 (1.51 to 373.78)	0 more per 1000 (from 0 more to 0 more)	VERY LOW
Mean number of wet nights per 3 weeks at the end of treatment	19	18	-	MD -15.99 (-20.78 to -11.2)	LOW
Number of drop outs at end of trial	4/19 (21.1%)	2/18 (11.1%)	RR 1.89 (0.39 to 9.11)	99 more per 1000 (from 68 fewer to 900 more)	VERY LOW

12.2.1.21 Enuresis alarm compared to enuresis alarm with intranasal desmopressin for children with severe wetting

One randomised controlled trial **Bradbury (1995)**¹⁸ compared enuresis alarms to enuresis alarms with 40 mcg intranasal desmopressin for children with severe wetting.

Table 12-23: Enuresis alarm compared to enuresis alarm and desmopressin for children with severe wetting - Clinical summary of findings

Outcome	Alarm	Alarm and desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 4 consecutive dry weeks	6/19 (31.6%)	14/21 (66.7%)	RR 0.47 (0.23 to 0.98)	354 fewer per 1000 (from 13 fewer to 514 fewer)	LOW
Mean number of wet nights per week at end of treatment (no SDs)	19	21	-	not pooled	LOW
Number of children relapsed at 6 months	2/19 (10.5%)	2/21 (9.5%)	RR 1.11 (0.17 to 7.09)	10 more per 1000 (from 79 fewer to 579 more)	LOW

12.2.1.22 Enuresis alarm and placebo compared to enuresis alarm with desmopressin for children with severe wetting

One randomised controlled trial **Leebeek (2001)**⁹¹ compared enuresis alarms and placebo to enuresis alarms with desmopressin for children with bedwetting.

Table 12-24: Enuresis alarm and placebo compared to enuresis alarm and desmopressin for children with bedwetting - Clinical summary of findings

Outcome	Alarm and placebo	Alarm and desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who had greater than 90% improvement in the mean number of wet nights per week at the end of treatment	18/38 (47.4%)	15/43 (34.9%)	RR 1.36 (0.8 to 2.3)	126 more per 1000 (from 70 fewer to 454 more)	LOW

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Number of children who had a 90% improvement in the number of dry nights at 6 month follow up	17/37 (45.9%)	17/41 (41.5%)	RR 1.11 (0.67 to 1.84)	46 more per 1000 (from 137 fewer to 349 more)	LOW
Mean number of wet nights per week at the end of treatment	39	43	-	not pooled	LOW

Study population- children with family and behavioural difficulties

12.2.1.23 Enuresis alarm compared to enuresis alarm with intranasal desmopressin for children with family and behavioural problems

One randomised controlled trial **Bradbury (1995)**¹⁸ compared enuresis alarms to enuresis alarms with 40 mcg intranasal desmopressin for children with family and behavioural problems.

Table 12 -25: Enuresis alarm compared to enuresis alarm and desmopressin for children with family and behavioural problems - Clinical summary of findings

Outcome	Alarm	Alarm and desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 4 consecutive dry weeks	4/14 (28.6%)	13/16 (81.3%)	RR 0.35 (0.15 to 0.83)	528 fewer per 1000 (from 138 fewer to 691 fewer)	LOW
Mean number of wet nights per week at end of treatment (no SDs)	14	16	-	not pooled	LOW
Number of children relapsed at 6 months	2/14 (14.3%)	2/16 (12.5%)	RR 1.14 (0.18 to 7.08)	17 more per 1000 (from 102 fewer to 760 more)	LOW

Study population- children with hearing impairment

12.2.1.24 Light enuresis alarm for children with hearing impairment with nocturnal enuresis

One observational study, **Baller (1970)**⁸ considered light enuresis alarms for children with hearing impairment with nocturnal enuresis. Children were treated with 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.

12.2.2 Network Meta-Analysis

Enuresis alarms were amongst the interventions included in a network meta-analysis of interventions used for nocturnal enuresis. The summary of results of this analysis is presented in chapter 24 and a detailed description of the analysis is presented in appendix F. If studies did not meet the inclusion criteria of the network meta-analysis protocol as stated in appendix F they were not included in the network meta-analysis.

12.2.3 Health economic evidence review

Given the lack of published evidence assessing the cost-effectiveness of different interventions, including enuresis alarms, used in the treatment of bedwetting, the GDG identified this area as high priority for original economic analysis. Therefore, a cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK National Health Service and Personal Social Services perspective. The time horizon for the analysis was 13 years, modelling patients from the time they entered at age 7 years until they reached age 20.

A summary of the analysis is provided below. The full report is presented in appendix G.

Summary of results

The results of the probabilistic sensitivity analysis are summarised in table 12-26 in terms of mean total costs and mean total QALYs and mean net benefit for each treatment sequence, where each mean is the average of 20,000 simulated estimates. The option with the greatest mean net benefit is the most cost-effective at a specified threshold (for example, £20,000). The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

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Table 12-26: Basecase probabilistic sensitivity analysis results

Treatment sequence	Mean cost	Mean QALYs	Net Benefit (threshold=£20,000 per QALY)	Probability that strategy is most cost-effective (threshold =£20,000 per QALY)
No Treatment	£0	19.734	£394,684	0.0%
Alarm - Imipramine	£206	19.901	£397,816	0.4%
Imipramine - Desmopressin	£406	19.914	£397,875	0.0%
Imipramine - Desmopressin - Desmopressin+Anticholinergic	£514	19.922	£397,929	0.0%
Desmopressin - Imipramine	£298	19.912	£397,943	0.7%
Imipramine - Alarm - Desmopressin	£374	19.927	£398,169	0.0%
Imipramine - Alarm - Desmopressin - Desmopressin+Anticholinergic	£434	19.932	£398,203	0.0%
Desmopressin - Alarm - Imipramine	£304	19.952	£398,729	0.3%
Alarm - Desmopressin - Imipramine	£275	19.955	£398,814	0.1%
Alarm - Imipramine - Desmopressin	£310	19.959	£398,877	0.0%
Alarm - Imipramine - Desmopressin - Desmopressin+Anticholinergic	£367	19.964	£398,910	0.0%
Desmopressin - Alarm+Desmopressin - Imipramine	£378	19.978	£399,178	3.1%
Desmopressin	£314	19.981	£399,297	7.1%
Alarm - Alarm+Desmopressin - Imipramine	£252	19.981	£399,357	13.1%
Desmopressin - Desmopressin+Anticholinergic	£426	19.990	£399,370	19.8%
Alarm - Desmopressin	£280	19.991	£399,549	4.9%
Desmopressin - Alarm+Desmopressin - Desmopressin	£410	19.998	£399,551	3.3%
Alarm - Desmopressin - Desmopressin+Anticholinergic	£346	19.997	£399,592	5.6%
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£433	20.002	£399,603	3.9%
Desmopressin - Alarm - Desmopressin	£350	19.998	£399,609	7.7%
Alarm - Alarm+Desmopressin - Desmo	£258	19.995	£399,640	15.9%
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£281	19.996	£399,647	8.3%
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£373	20.001	£399,647	5.8%

The results of the incremental analysis in the probabilistic analysis, excluding dominated and extendedly dominated strategies, are presented in table 12-27.

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Table 12-27: Incremental analysis of basecase probabilistic results with dominated and extendedly dominated sequences removed

Treatment sequence	Mean cost (£)	Incremental Cost (£)	Mean QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		19.73421		
Alarm - Alarm+Desmopressin - Desmo	£258	£258	19.99489	0.26068	£988
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£282	£24	19.9964	0.00151	£15,828
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£373	£91	20.00099	0.00459	£19,891
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£433	£61	20.00183	0.00084	£72,143

The GDG considered that the differences between intervention sequences were relatively small and the probabilistic results indicated substantial uncertainty around the mean cost and benefit estimates. Small changes to the model inputs appears to result in substantial changes to the conclusions about modelled sequences' relative and overall cost-effectiveness.

A series of sensitivity analyses were undertaken to test some of the assumptions feeding into the model and none of these affected the cost-effectiveness of the sequence alarm followed by combined alarm and desmopressin and then desmopressin alone compared to no treatment.

The economic analysis conducted and presented here represents the first undertaken to assess the cost-effectiveness of interventions used in the treatment of children with bedwetting. And although the analysis is directly applicable to decision making in the UK NHS, it has some potentially serious limitations, some of which may significantly impact the overall conclusions that can be drawn. The main limitations of the analysis are related to the fact that assumptions had to be made in the absence of evidence. Some of these key assumptions centre around:

- treatment effectiveness being independent of age
- health care resource use having been estimated by GDG
- utility weights having been estimated by GDG

A full discussion of these can be found in appendix G.

12.2.4 Evidence statements

Studies which included children with bedwetting and possible daytime symptoms

Enuresis alarm compared to no treatment

Baker (1969)⁷, Bollard (1981)¹⁵, Bollard (1982)¹⁶, Houts (1986)⁷³, Jehu (1977)⁷⁵, Moffatt (1987)¹⁰³

- Six studies showed that more children achieved 14 consecutive dry nights with enuresis alarm treatment than with no treatment. Relative risk 16.9, 95% CI 7.17, 39.85. Children had a mean age of 8.1 to 10.05 years and the length of treatment was 10 to 20 weeks.

Bollard (1982)¹⁶

- One study showed that children treated with an enuresis alarm had 3.8 fewer wet nights in the final week of treatment compared to those who had no treatment. Children had a mean age of 8.6 to 9.7 years and the length of treatment was 20 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Houts (1986)⁷³, Jehu (1977)⁷⁵

- Two studies showed there was no statistically significant difference in the number of children who dropped out of the trial when placed in the enuresis alarm treatment group compared to the no treatment group. Relative risk 4.16, 95% CI 0.5, 34.6. Children had a mean age of 8.35 to 10.05 years and the length of treatment was 12 to 18 weeks.

Unsupervised enuresis alarm compared to supervised enuresis alarm

Bollard (1981)¹⁵

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights with a supervised enuresis alarm (weekly telephone contact with parent) than with an unsupervised enuresis alarm. Relative risk 1.33, 95% CI 0.82, 2.16. Children had a mean age of 9 years and 8 months and the length of treatment was 20 weeks.
- One study reported that children treated with a supervised enuresis alarm had 0.4 fewer wet nights in the final week of treatment compared to those

who treatment with an unsupervised enuresis alarm. Children had a mean age of 9 years and 8 months and the length of treatment was 20 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Enuresis alarm compared to other single treatments

Kolvin (1972)⁸³

- One study showed there was no statistically significant difference in the number of children who had an 80% improvement in the number of dry when treated with imipramine compared to enuresis alarm treatment. Relative risk 1.16, 95% CI 0.71, 1.89. Children had a mean age of 9 years and 4 months and the length of treatment was 2 months. (Kolvin (1972) (Kolvin et al. 715-26) did not state the dose of imipramine given to children)
- One study showed that children treated with an enuresis alarm had 1.1 fewer wet nights per week at follow up compared to those treated with imipramine. Children had a mean age of 9 years and 4 months and the length of treatment was 2 months. (Kolvin (1972) (Kolvin et al. 715-26) did not state the dose of imipramine given to children). No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Fournier (1987)⁶⁰, Kolvin (1972)⁸³

- Two studies evaluated the number of wet nights in the final week of treatment, one study showed no difference and one showed children treated with imipramine had 0.4 fewer wet nights than those treated with an enuresis alarm. Children in Kolvin (1972) (Kolvin et al. 715-26) had a mean age of 9 years and 4 months and the length of treatment was 2 months, children in Fournier (1987) (Fournier et al. 849-53) had a mean age of 8.5 years and the length of treatment was 6 weeks. Fournier (1987) (Fournier et al. 849-53) gave 25 mg imipramine to children, Kolvin (1972) (Kolvin et al. 715-26) did not state the dose of imipramine given to children. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Danquah (1975)³⁸

- One study showed that children treated with an enuresis alarms had 0.8 fewer wet nights in the final week of treatment compared to those treated with enuresis amitriptyline. Children had a mean age of 10.4 years and the length of treatment was 7 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Enuresis alarm compared to enuresis alarm plus star charts

van Londen (1993)¹⁵⁶

- One study showed that more children achieved 14 consecutive dry nights with enuresis alarm plus a star chart with rewards for correct behaviour (for waking up to the enuresis alarm within 3 mins, going to the toilet after, returning to bed and resetting the enuresis alarm) and returning a sticker if correct behaviour not demonstrated than with enuresis alarm alone treatment. Relative risk 0.74, 95% CI 0.6, 0.91. Children had a mean age of 8.6 years and the length of treatment was 20 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed at 2.5 years in children treated with enuresis alarm plus a star chart with rewards for correct behaviour (for waking up to the enuresis alarm within 3 mins, going to the toilet after, returning to bed and resetting the enuresis alarm) and returning a sticker if correct behaviour not demonstrated than enuresis alarm alone. Relative risk 1.85, 95% CI 0.96, 3.56. Children had a mean age of 8.6 years and the length of treatment was 20 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between treated with an enuresis alarm and children treated with an enuresis alarm plus a star chart with reward for a dry night and returning a sticker for a wet night. Relative risk 0.85, 95% CI 0.67, 1.09. Children had a mean age of 8.6 years and the length of treatment was 20 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed at 2.5 years between children treated with an enuresis alarm and children treated with an enuresis alarm plus a star chart with reward for a dry night and returning a sticker for a wet night. Relative risk 1.1, 95% CI 0.64, 1.88. Children had a mean age of 8.6 years and the length of treatment was 20 weeks.

- One study showed that more children achieved 14 consecutive dry nights with an enuresis alarm plus a star chart with rewards for correct behaviour (for waking up to the enuresis alarm within 3 months, going to the toilet after, returning to bed and resetting the enuresis alarm) and returning a sticker if correct behaviour not demonstrated than with an enuresis alarm plus a star chart with reward for a dry night and returning a sticker for wet a night. Relative risk 0.87, 95% CI 0.75, 1. Children had a mean age of 8.6 years and the length of treatment was 20 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed at 2.5 years between children treated with an enuresis alarm plus a star chart with rewards for correct behaviour (for waking up to the enuresis alarm within 3 months, going to the toilet after, returning to bed and resetting the enuresis alarm) and returning a sticker if correct behaviour not demonstrated and children treated with an enuresis alarm plus a star chart with reward for a dry night and returning a sticker for a wet night. Relative risk 1.68, 95% CI 0.88, 3.22. Children had a mean age of 8.6 years and the length of treatment was 20 weeks.

Enuresis alarm compared to enuresis alarm in combination with another treatment

Bradbury (1995) ¹⁸

- One study showed there was no statistically significant difference in the number of children achieving 14 consecutive dry nights with enuresis alarm treatment than with 40 mcg intranasal desmopressin and enuresis alarm treatment. Relative risk 0.72, 95% CI 0.51, 1.03. Children had a mean age of 9.7 to 10 years and the length of treatment was 6 weeks.
- One study showed that children treated with 40 mcg intranasal desmopressin and enuresis alarm had 1.3 fewer wet nights in the final week of treatment compared to those who had enuresis alarm alone treatment. Children had a mean age of 9.7 to 10 years and the length of treatment was 6 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed there was no statistically significant difference in relapse at 6 months in children when treated with an enuresis alarm compared to enuresis alarm and 40 mcg intranasal desmopressin. Relative risk 1.27, 95% CI 0.32, 4.95. Children had a mean age of 9.7 to 10 years and the length of treatment was 6 weeks.

- One study showed there was no statistically significant difference in the number of children who dropped out of the trial when placed in the 40 mcg intranasal desmopressin and enuresis alarm treatment group compared to the enuresis alarm alone treatment group. Relative risk 5.14, 95% CI 0.26, 103.37. Children had a mean age of 9.7 to 10 years and the length of treatment was 6 weeks.

Sukhai (1989)¹⁴⁴

- One study showed children treated with enuresis alarm and desmopressin had 1 fewer wet night per week at the end of treatment compared to children treated with enuresis alarm and placebo. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 11 years and the length of treatment was 2 weeks.

Fournier (1987)⁶⁰

- One small study showed children treated with an imipramine and enuresis alarm had 1.5 fewer wet nights in the final week of treatment compared to those who had enuresis alarm alone treatment. Children had a mean age of 8.5 years and the length of treatment was 6 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Bennett (1985)¹¹

- One study showed there was no statistically significant difference in the number of children that achieved 14 consecutive dry nights with enuresis alarm alone than with dry bed training and enuresis alarm treatment. Relative risk 0.89, 95% CI 0.34, 2.32. Children had a mean age of 8.5 years and had 12 weeks of treatment.
- One study showed there was no statistically significant difference in the mean number of wet nights per week at the end of treatment between children treated with enuresis alarms and children treated with dry bed training and an enuresis alarm. Mean difference -0.4, 95% CI -2.09, 1.29.
- One study showed there was no difference in the number of children who dropped out between children treated with enuresis alarms and children treated with dry bed training and an enuresis alarm. Relative risk 1, 95% CI 0.53, 1.89.

Fielding (1980)⁵⁶, Geffken (1986)⁶², Houts (1986)⁷³

- Three studies (1 of which had 2 subgroups) showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights with enuresis alarm alone treatment than with retention control training and enuresis alarm treatment. Relative risk 0.84, 95% CI 0.68, 1.04. Children in Fielding (1980) had a mean age of 7.96 to 9.08 years and the length of treatment was 14 weeks. Children in Geffken (1986) had an age range of 5 to 13 years and the length of treatment was 14 weeks; children in Houts (1986) (Houts, Peterson, and Whelan 462-69) had a mean age of 8.35 to 9.06 years and the length of treatment was 16 weeks.

Geffken (1986)⁶²

- One study (which had 2 subgroups) showed that children treated with retention control training and an enuresis alarm had 0.3 and 0.4 fewer wet nights in the final week of treatment compared to those who had enuresis alarm alone treatment. Children had an age range of 5 to 13 years and the length of treatment was 14 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study (which had 2 subgroups) showed that children treated with retention control training and an enuresis alarm had 1.5 and 0.4 fewer wet nights at follow up compared to those who had enuresis alarm alone treatment. Children had an age range of 5 to 13 years and the length of treatment was 14 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Fielding (1980)⁵⁶, Houts (1986)⁷³

- Two studies showed there was no statistically significant difference in the number of children who relapsed at 6 months between the group treated with a retention control training and enuresis alarm and those treated with an enuresis alarm alone. Relative risk 0.92, 95% CI 0.42, 2.02. Children in Fielding (1980) had a mean age of 7.96 to 9.08 years and the length of treatment was 14 weeks. Children in Houts (1986) had a mean age of 8.35 to 9.06 years and the length of treatment was 16 weeks.
- Two studies showed there was no statistically significant difference in the number of children who relapsed at 12 months between the group treated with a retention control training and enuresis alarm and those treated with

an enuresis alarm alone. Relative risk 0.82, 95% CI 0.38, 1.77. Children in Fielding (1980) had a mean age of 7.96 to 9.08 years and the length of treatment was 14 weeks. Children in Houts (1986) had a mean age of 8.35 to 9.06 years and the length of treatment was 16 weeks.

Houts (1986) (Houts, Peterson, and Whelan 462-69)

- One study showed there was no statistically significant difference in children who dropped out of the trial when placed in the enuresis alarm treatment group compared to the retention control training and enuresis alarm group. Relative risk 1.5, 95% CI 0.29, 7.73. Children had a mean age of 8.35 to 9.06 years and the length of treatment was 16 weeks.

Studies included children with bedwetting only

Enuresis alarm compared to no treatment

Lynch (1984)⁹⁵, Nawaz (2002)¹¹¹, Wagner (1982)¹⁶⁰, Wagner (1985)¹⁶²

- Four studies showed that more children achieved 14 consecutive dry nights with enuresis alarm treatment than with no treatment. Relative risk 7.35, 95% CI 2.56, 21.11. Children had a mean age of 7.9 to 9.93 years and the length of treatment was 10 to 16 weeks.

Lynch (1984)⁹⁵, Nawaz (2002)¹¹¹

- Two studies showed that children treated with an enuresis alarm had fewer wet nights in the final week of treatment compared to those who had no treatment. Mean difference -2.78, 95% CI -4.42, -1.14. Children in Lynch (1984) had an age range of 5 to 12 years and length of treatment was 10 weeks; children in Nawaz (2002) had a mean age of 9.84 and 9.93 years and the length of treatment was 6 weeks.

Wagner (1982)¹⁶⁰, Wagner (1985)¹⁶²

- Two studies showed there was no statistically significant difference in the number of children who relapsed between children treated with an enuresis alarm and children who had no treatment. Relative risk 0.54, 95% CI 0.24, 1.19. Children had a mean age of 7.9 years and length of treatment was 12 weeks.

Lynch (1984)⁹⁵

- One study showed there was no difference in the number of children who dropped out of the trial when placed in the enuresis alarm treatment group compared to the no treatment group. Relative risk 1, 95% CI 0.16, 6.42. Children had an age range of 5 to 12 years and the length of treatment was 10 weeks.

Pad and bell enuresis alarm compared to body worn enuresis alarm

Butler (1990)²⁶

- One study showed there was no difference in the number of children who achieved 14 consecutive dry nights between children treated with body worn enuresis alarm and children treated with a pad and bell enuresis alarm. Relative risk 1, 95% CI 0.67, 1.5. Children had a mean age of 8.11 to 10.6 years and the length of treatment was 16 weeks.
- One study showed children treated with body worn enuresis alarm had 0.2 fewer wet nights than those treated with pad and bell enuresis alarm. Children had a mean age of 8.11 to 10.6 years and the length of treatment was 16 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed there was no statistically significant difference in the number of children who relapsed at 6 months between the group treated with a body worn enuresis alarm and those treated with a pad and bell enuresis alarm. Relative risk 1.33, 95% CI 0.36, 4.90. Children had a mean age of 8.11 to 10.6 years and the length of treatment was 16 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out of the trial when placed in a group treated with a body worn enuresis alarm and those treated with a pad and bell enuresis alarm. Relative risk 1.50, 95% CI 0.28, 8.04. Children had a mean age of 8.11 to 10.6 years and the length of treatment was 16 weeks.

Enuresis alarm compared to single other treatment for children with bedwetting

Ng (2005)¹¹⁵

- One study showed there was no statistically significant difference in the number of children achieved 14 consecutive dry nights between children treated with an enuresis alarm and children treated with desmopressin. Relative risk 0.54, 95% CI 0.27, 1.11. Children were aged over 6 years and the

length of treatment was 3 months. Ng (2005) considered 0.2 mg tablet desmopressin.

Wille (1986)¹⁶⁷

- One study showed there was no statistically significant difference in the number of children achieved only 5 wet nights in 28 nights between children treated with an enuresis alarm and children treated with desmopressin. Relative risk 1.22, 95% CI 0.9, 1.66. Children were aged over 6 years and the length of treatment was 3 months. Wille (1986) considered 200 micro
- One study showed that there was a 78% rate of false enuresis alarms during the trial. Children were aged over 6 years and the length of treatment was 3 months. Wille (1986) considered 200 micro grams intranasal desmopressin.

Ng (2005)¹¹⁵, **Wille (1986)**¹⁶⁷

- Two studies showed there was no statistically significant difference in the number of wet nights in the final week of treatment of those treated with an enuresis alarm compared to those treated with desmopressin. Mean difference -0.46, 95% CI -1.53, 0.62. Children were aged over 6 years and the length of treatment was 3 months. Ng (2005) considered 0.2 mg tablet desmopressin and Wille (1986) considered 200 micro grams intranasal desmopressin.
- One study, Wille (1986), showed that children treated with desmopressin had a faster response compared to children treated with an enuresis alarm. Wille (1986) considered a response to be the number of dry nights.
- One study, Ng (2005), showed that children treated with an enuresis alarm had a faster response compared to children treated with desmopressin. Ng (2005) considered a response to be a reduction in the number of wet nights.
- Two studies showed after treatment children treated with an enuresis alarm had a continued higher response compared to children treated with desmopressin. Ng (2005) considered a response to be a reduction in the number of wet nights and Wille (1986) considered a response to be the number of dry nights. Children were aged over 6 years and treatment was for 3 months. Ng (2005) considered 0.2 mg tablet desmopressin and Wille (1986) considered 200 micro grams intranasal desmopressin.
- Two studies showed children treated with desmopressin were more likely to relapse at 3 months compared to children treated with enuresis alarms.

Relative risk 0.09, 95% CI 0.02, 0.45. Children had a mean age of 9.5 years and the length of treatment was 12 weeks. Ng (2005) considered 0.2 mg tablet desmopressin.

- Two studies showed there was no statistically significant difference in the number of children who dropped out of the trial when placed in the enuresis alarm treatment group compared to the desmopressin treatment group. Relative risk 3.69, 95% CI 0.95, 14.33. Children were aged over 6 years and the length of treatment was 3 months. Ng (2005) considered 0.2 mg tablet desmopressin and Wille (1986) considered 200 micro grams intranasal desmopressin.

Wagner (1982)¹⁶⁰

- One study showed children treated with an enuresis alarm were more likely to achieve 14 consecutive dry nights compared to children treated with imipramine treatment. Relative risk 2.5, 95% CI 1.08, 5.79. Children had a mean age of 7.9 years and the length of treatment was 14 weeks. Wagner (1982) gave 25 mg imipramine for children < 32 kg, 50 mg imipramine for children > 32k g.
- One study showed that children treated with an enuresis alarm had 2.17 fewer wet nights in the final week of treatment than those treated with imipramine. Children had a mean age of 7.9 years and the length of treatment was 14 weeks. Wagner (1982) gave 25 mg imipramine for children < 32 kg, 50 mg imipramine for children > 32k g. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed there was no statistically significant difference in the number of children relapsing at 6 months when treated with an enuresis alarm compared to imipramine. Relative risk 0.56, 95% CI 0.29, 1.07. Children had a mean age of 7.9 years and the length of treatment was 14 weeks. Wagner (1982) gave 25 mg imipramine for children < 32 kg, 50 mg imipramine for children > 32k g.

Enuresis alarm compared to enuresis alarm in combination with other treatments

Ng (2005)¹¹⁵

- One study showed more children treated with enuresis alarm and desmopressin achieved 14 consecutive dry nights compared to those treated

with enuresis alarm treatment. Relative risk 0.37, 95% CI 0.19, 0.71. Children had a mean age of 9.5 years and the length of treatment was 12 weeks. Ng (2005) considered 0.2 mg tablet desmopressin.

- One study showed children treated with enuresis alarm and desmopressin had fewer wet nights per week at the end of treatment compared to children treated with enuresis alarm alone. Mean difference 1.5, 95% CI 0.43, 2.57. Children had a mean age of 9.5 years and the length of treatment was 12 weeks. Ng (2005) considered 0.2 mg tablet desmopressin.
- One study showed there was no statistically significant difference in the number of children who relapsed at 3 months between children treated with an enuresis alarm and children treated with an enuresis alarm and desmopressin. Relative risk 0.16, 95% CI 0.01, 2.44. Children had a mean age of 9.5 years and the length of treatment was 12 weeks. Ng (2005) considered 0.2 mg tablet desmopressin.
- One study showed there was no statistically significant difference in the number of children who dropped out of the trial when placed in the desmopressin and enuresis alarm treatment group compared to the enuresis alarm alone treatment group. Relative risk 2.13, 95% CI 0.6, 7.56. Children had a mean age of 9.5 years and the length of treatment was 12 weeks. Ng (2005) considered 0.2 mg tablet desmopressin.

Nawaz (2002) ¹¹¹

- One study showed there was no statistically significant difference in the number of children that achieved 14 consecutive dry nights with enuresis alarm alone than with dry bed training and enuresis alarm treatment. Relative risk 0.38, 95% CI 0.13, 1.08. Children had a mean age of 9.93 years and the length of treatment was 16 weeks.
- One study showed children treated with dry bed training and an enuresis alarm had fewer wet nights per week at the end of treatment compared to children treated with an enuresis alarm. Mean difference 2.42, 95% CI 0.71, 4.13. Children had a mean age of 9.93 years and the length of treatment was 16 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed at 6 months in children treated with dry bed training with an enuresis alarm compared to enuresis alarm alone. Relative risk 2.67, 95% CI 0.23, 30.4. Children had a mean age of 9.93 years and the length of treatment was 16 weeks.

Fielding (1980)⁵⁶

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights with enuresis alarm alone treatment than with retention control training and enuresis alarm treatment. Relative risk 1.2, 95% CI 0.81, 1.78. Children had a mean age of 7.96 to 9.08 years and the length of treatment was 14 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed at 6 months between the group treated with a retention control training and enuresis alarm and those treated with an enuresis alarm alone. Relative risk 1.31, 95% CI 0.4, 4.32. Children had a mean age of 7.96 to 9.08 years and the length of treatment was 14 weeks.
- One study showed there was no statistically significant difference in the number of children who relapsed at 12 months between the groups treated with a retention control training and enuresis alarm and those treated with an enuresis alarm alone. Relative risk 1.57, 95% CI 0.64, 3.88. Children had a mean age of 7.96 to 9.08 years and the length of treatment was 14 weeks.

Studies included children with monosymptomatic nocturnal enuresis

Enuresis alarm compared to desmopressin for children

Longstaffe (2000)⁹², **Tuygun (2007)**¹⁵¹

- Two studies showed there was no statistically significant difference in the number of children achieved 14 consecutive dry nights with desmopressin than with enuresis alarm treatment. Relative risk 1.16, 95% CI 0.89, 1.5. Children were aged over 7 years and the length of treatment was 3 to 6 months. Longstaffe (2000) considered 200 micro grams intranasal desmopressin, and Tuygun (2007) considered 20 to 40 micro grams intranasal desmopressin or 0.2 to 0.4 mg tablet desmopressin.

Tuygun (2007)¹⁵¹

- One study showed there was no statistically significant difference in the number of children who had a 50 to 90% improvement in the number of dry nights when treated with desmopressin compared to enuresis alarm treatment. Relative risk 0.84, 95% CI 0.42, 1.7. Children had a median age of 8 years and the length of treatment was 3 months. Tuygun (2007) considered 20 to 40 micro grams intranasal desmopressin or 0.2 to 0.4 mg tablet desmopressin.

- One study showed that children treated with an enuresis alarm had fewer wet nights in the final month of treatment compared to those in the desmopressin group. Mean difference -7.29, 95% CI -11.27, -3.31. Children had a median age of 8 years and the length of treatment was 3 months. Tuygun (2007) considered 20 to 40 micro grams intranasal desmopressin or 0.2 to 0.4 mg tablet desmopressin.
- One study showed that fewer children relapse at 6 months when treated during 3 months with an enuresis alarm compared to desmopressin. Relative risk 0.52, 95% CI 0.29, 0.93. Children had a median age of 8 years and the length of treatment was 3 months. Tuygun (2007) considered 20 to 40 micro grams intranasal desmopressin or 0.2 to 0.4 mg tablet desmopressin.

Longstaffe (2000)⁹²

- One study showed that giving children treatment for nocturnal enuresis improved their psychological scores in both treatment groups. Children were age over 7 years and the length of treatment was 6 months. Longstaffe (2000) considered 200 micro grams intranasal desmopressin.
- One study showed there was no statistically significant difference in the number of children who dropped out of the trial when placed in the enuresis alarm treatment group compared to the desmopressin treatment group. Relative risk 1.57, 95% CI 0.55, 4.54. Children were age over 7 years and the length of treatment was 6 months. Longstaffe (2000) considered 200 micro grams intranasal desmopressin.

Enuresis alarm compared to enuresis alarm with desmopressin

Ozden (2008)¹¹⁷

- One study showed there was no statistically significant difference the number of children who achieved a greater than 75% reduction in the number of wet nights between the children treated with desmopressin and enuresis alarm and those who had enuresis alarm alone treatment. Relative risk 1.59, 95% CI 0.62, 4.08. Children had a mean age of 10.1 years and the length of treatment was 6 weeks.
- One study showed children treated with an enuresis alarm and desmopressin had fewer wet nights per week at the end of treatment compared to children treated with an enuresis alarm. Mean difference 0.5, 95% CI 0.19, 0.81. Children had a mean age of 10.1 years and the length of treatment was 6 weeks.

- One study showed there was no statistically significant difference in the number of children who dropped out of the trial when placed in the desmopressin and enuresis alarm treatment group compared to the enuresis alarm alone treatment group. Relative risk 2.27, 95% CI 0.61, 8.52. Children had a mean age of 10.1 years and the length of treatment was 6 weeks.

Studies included children with severe wetting

Enuresis alarm compared to no treatment for children

Ronen (1992) (Ronen, Wozner, and Rahav 1-14)

- One study showed that more children achieved 14 consecutive dry nights with an enuresis alarm compared to children who had no treatment. Relative risk 23.75, 95% CI 1.51, 373.78. Children had a mean age of 10.5 (sd 2.28) years and the length of treatment was 3 weeks.
- One study showed that children treated with an enuresis alarm had fewer wet nights per 3 weeks at the end of treatment compared to those who had no treatment. Mean difference -15.99, 95% CI -20.78, -11.2. Children had a mean age of 10.5 (sd 2.28) years and the length of treatment was 3 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with an enuresis alarm and children who had no treatment. Relative risk 1.89, 95% CI 0.39, 9.11. Children had a mean age of 10.5 (sd 2.28) years and the length of treatment was 3 weeks.

Enuresis alarm compared to enuresis alarm with intranasal desmopressin

Bradbury (1995)¹⁸

- One study showed that more children achieved 14 consecutive dry nights with 40 mcg intranasal desmopressin and enuresis alarm treatment than with enuresis alarm treatment. Relative risk 0.47, 95% CI 0.23, 0.98. Children had a mean age of 9.7 to 10 years and the length of treatment was 6 weeks.
- One study showed that children treated with 40 mcg intranasal desmopressin and enuresis alarm had 2 fewer wet nights in the final week of treatment compared to those who had enuresis alarm alone treatment. Children had a mean age of 9.7 to 10 years and the length of treatment was 6 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

- One study showed there was no statistically significant difference in the number of children who relapsed at 6 months in children treated with 40 mcg intranasal desmopressin and enuresis alarm compared to enuresis alarm alone. Relative risk 1.11, 95% CI 0.17, 7.09. Children had a mean age of 9.7 to 10 years and the length of treatment was 6 weeks.

Enuresis alarm and placebo compared to enuresis alarm with desmopressin

Leebeek (2001) ⁹¹

- One study showed there was no statistically significant difference in the number of children who had a 90% improvement in the number of dry nights between children treated with enuresis alarm and placebo and children treated with enuresis alarm and desmopressin. Relative risk 1.36, 95% CI 0.8, 2.3. Children had an age range of 6 to 14 years and the length of treatment was 6 weeks.
- One study showed there was no statistically significant difference in the number of children who had a 90% improvement in the number of dry nights at 6 month follow up between children treated with enuresis alarm and placebo and children treated with enuresis alarm and desmopressin. Relative risk 1.11, 95% CI 0.67, 1.84. Children had an age range of 6 to 14 years and the length of treatment was 6 weeks.
- One study showed children treated with an enuresis alarm and placebo had 0.56 fewer wet nights per week compared to children treated with enuresis alarm and desmopressin. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had an age range of 6 to 14 years and the length of treatment was 6 weeks.

Studies included children with family and behavioural problems

Enuresis alarm compared to enuresis alarm with intranasal desmopressin

Bradbury (1995) ¹⁸

- One study showed that more children achieved 14 consecutive dry nights with 40 mcg intranasal desmopressin and enuresis alarm treatment than with enuresis alarm treatment. Relative risk 0.35, 95% CI 0.15, 0.83. Children had a mean age of 9.7 to 10 years and the length of treatment was 6 weeks.
- One study showed that children treated with 40 mcg intranasal desmopressin and enuresis alarm had 4.5 fewer wet nights in the final week

of treatment compared to those who had enuresis alarm alone treatment. Children had a mean age of 9.7 to 10 years and the length of treatment was 6 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

- One study showed there was no statistically significant difference in the number of children who relapsed at 6 months in children treated with 40 mcg intranasal desmopressin and enuresis alarm compared to enuresis alarm alone. Relative risk 1.14, 95% CI 0.18, 7.08. Children had a mean age of 9.7 to 10 years and the length of treatment was 6 weeks.

Studies included for children with hearing impairment

Light enuresis alarm for children with hearing impairment

Baller (1970) ⁸

- One observational study showed all children 21 treated with the light enuresis alarm gained complete dryness (10 consecutive dry nights) within 30 nights. Children had an age range of 7 to 16 years and had 30 nights of treatment.
- One observational study showed 1 child relapsed but after 2 more treatments with the light enuresis alarm he gained dryness. Children had an age range of 7 to 16 years and had 30 nights of treatment.

NCGC network meta-analysis (see appendix F)

For children with bedwetting and possible daytime symptoms

- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with alarm and no treatment / placebo. Relative risk 8.601, 95% CI 7.294, 9.103. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**

For children with bedwetting only

- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with alarm and no treatment / placebo. Relative risk 8.601, 95% CI 7.294, 9.103. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**

- **The NCGC NMA showed there was a statistically significant difference in the number of children who experienced a recurrence of bedwetting at 6 months between children treated with alarm and no treatment / placebo. Relative risk 0.0364, 95% CI 0.005, 0.840. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**

For estimates of treatment effect relative to other active comparators, please see section 24.4 in chapter 24.

12.2.5 Health economic evidence statements

NCGC economic evaluation (see appendix G)

- **Alarms are a cost-effective initial intervention even if they need to be replaced at least once during a course of treatment. This evidence has potentially serious limitations and direct applicability.**
- **An intervention sequence starting with alarm (and followed by combined alarm and desmopressin and then by desmopressin alone) is cost-effective in the treatment of children with bedwetting starting at age 5 or 7 years. This evidence has potentially serious limitations and direct applicability.**

12.2.6 Evidence to recommendations

Relative values of different outcomes

The GDG considered that sustained dryness was the outcome wished for by children and their parents or carers. This was represented by the outcome of 14 consecutive dry nights to show initial success and indicate the effectiveness of the treatments being evaluated. The mean number of wet nights was also considered by the GDG in evaluating the effectiveness of treatments. Outcomes such as relapse and follow up rates were considered to evaluate sustained dryness.

Trade off between clinical benefit and harms

No evidence was identified of harms of alarm treatment.

Economic Considerations

Enuresis alarms were evaluated as part of original economic modelling undertaken for this guideline and were shown to be a likely cost-effective first line treatment option. The analysis showed that there was considerable uncertainty about which intervention was the most cost-effective first line option, and this was likely caused by the uncertainty around estimates of treatment effectiveness observed in the pair-

wise and network meta-analyses. The GDG considered that given the substantial uncertainty between interventions, it would be reasonable to recommend first line treatment with alarm as it was consistently shown to be among less costly and still effective options.

As children who have previously responded to alarm are likely to respond to it again, it would be a good use of NHS resources to encourage children and families to retain their alarm and reuse it before trying other options that have associated costs. The economic model assumed that prescribed alarms were given, not loaned, to patients and under this assumption, repeat use of alarms was considered cost-effective. And, even if all alarms must be replaced at least once during treatment, they are still considered to be a cost-effective intervention.

Alarms are likely to be considered to be a cost-effective first-line treatment regardless of age at initiation.

Quality of evidence (this includes clinical and economic)

The quality of evidence for the outcomes preferred by the GDG was generally low. The individual direct comparisons found in the evidence review were of underpowered studies with small sample sizes. Some studies did not give standard deviations and therefore mean difference and CI could not be calculated giving incomplete evidence.

The GDG considered that the available evidence on alarms compared to no treatment contained inadequate description of the study groups, mainly in terms of the patients' age and the number of girls included in studies. One study compared supervised alarms to unsupervised alarms; the GDG considered that the type of supervision involved in the studies was not part of common clinical practice in England and Wales.

Other considerations

The GDG considered the direct evidence, the network meta-analysis and the health economic evidence in making their recommendations. They considered that the evidence from the direct comparisons indicated that alarms and desmopressin had similar effects on dryness (both complete dryness and reduced number of wet nights) when receiving treatment but children were more likely to have recurrence of bedwetting following use of desmopressin. In the study that examined monosymptomatic enuresis desmopressin had a faster response (described in Ng (2005)¹¹⁵ as reduction in the number of wet nights, described in Wille (1986)¹⁶⁷ as the number of dry nights); however alarms had more continued success and children were less likely to experience a recurrence of bedwetting. The GDG considered that when children and families consult with healthcare professionals about bedwetting

they are seeking a 'cure' from bedwetting. Pharmacological agents have an effect on bedwetting primarily while the child is taking them and do not affect the underlying pathophysiology; alarms develop a conditioned response of waking in response to full bladder which is more likely to continue after alarm treatment.

The evidence of continued success associated with alarms from the evidence review and from professional experience of the GDG was pivotal in the GDG decision to recommend alarms as the choice for first line treatment if the child and family could use alarm. The GDG considered that the first line use of an alarm as a non-pharmacological intervention in children was also perceived as an advantage. The patient carer members specifically highlighted concern about using pharmacological interventions in young children if alternatives are available.

Children with special needs

There was no evidence one type of alarm was better than another type of alarm. The GDG considered that if different alarms were available children and families should be given choice. The evidence also indicated that alarms have been used successfully as treatment in children with hearing problems and children with behavioural problems. The GDG considered it important that these children do not lose out on a potentially good treatment modality and where possible, and with the needs of the child and family considered, alarms should be considered as treatment.

Children with and without daytime symptoms

The GDG were interested in whether there was any difference in response to alarm among population groups with different wetting patterns i.e. population who did or did not have daytime wetting. The evidence indicated that bedwetting in children who also had daytime wetting did respond to alarm and there was no difference in the number achieving 14 consecutive dry nights when alarm was compared with enuresis and desmopressin. The GDG considered it important that children with daytime wetting did have access to alarm treatment and made a recommendation to ensure that alarm is considered as an option for these children. No specific evidence was found regarding treatment of secondary enuresis but the professional experience of the GDG was that these children do respond similarly to children with primary enuresis.

Children who are very infrequent bedwetters will not wet often enough to have the conditioned responses by which an alarm works.

Assessment at 4 weeks

The GDG discussed the lack of evidence for when a patient should be assessed after starting treatment. From clinical experience the GDG discussed the benefits of following up early at 4 weeks or less to encourage the patient and report on progress with the treatment. The GDG made a consensus decision on assessment at 4 weeks after starting treatment. In younger children it may be advisable to stop at this stage as child may respond when older and proceeding with treatment for longer at this stage may engender negativity in child and family about the alarm.

Continue alarm until minimum of 2 weeks uninterrupted dryness has been achieved

The GDG discussed the lack of evidence for how long the alarm should be used. The GDG discussed from clinical experience that to ensure continuing success it was important the patient continued to use the alarm until 14 consecutive dry nights was achieved to reduce the chance of experiencing a recurrence of bedwetting after treatment.

Review at 3 months

The GDG considered that it can take several weeks for an alarm to have an effect and it is important to inform and encourage the family to use it for some weeks to get an effect. However a child not getting any response from an alarm should stop the alarm and the GDG considered it not appropriate to continue beyond 3 months if there was not continuing improvement. The use of an alarm can be difficult for a family and an assessment of motivation and ability to continue its use should be made.

Addition of reward systems

The evidence supported the addition of reward systems to alarms and this finding is consistent with psychological theory. The GDG considered that as part of the instructions in how to use the alarm it might be useful to suggest to the family and help them to consider how they will approach this.

Use of alarm in children between 5 and 7

While the GDG considered that children between 5 and 7 years may not require treatment those that do, and are appropriately motivated and mature enough to cope with an alarm should not be denied use of an alarm by virtue of age alone.

Combination of alarm and pharmacological treatments

The direct evidence indicated that combination of alarms with desmopressin were similarly effective to alarms alone in the number of wet nights at end of treatment and drop out rates for children with MNE but relapse rates were inconclusive for children with bedwetting and possible daytime symptoms. The GDG did not consider the evidence supportive of using combination treatment as first line although the evidence indicated this may be better for children with severe wetting and may also be helpful for children with behavioural difficulties.

The evidence comparing alarms to imipramine was two small studies with some contradictory findings (for number of wet nights at the end of treatment). Alarms had fewer wet nights at follow up compared to imipramine. The addition of imipramine to an alarm was not supported by clinical evidence.

12.2.7 Recommendations (on offering and treatment)

12.2.7.1 *Offer an alarm as the first-line treatment to children with bedwetting, unless:*

- *an alarm is considered undesirable to the child or parents and carers*
or
- *an alarm is considered inappropriate, particularly if:*
 - *the child has very infrequent bedwetting (that is, less than 1–2 wet beds per week)*
 - *the parents or carers are having emotional difficulty coping with the burden of bedwetting*
 - *the parents or carers are expressing anger, negativity or blame towards the child.[1.8.1]*

12.2.7.2 *Assess the response to an alarm by 4 weeks and continue with treatment if the child is showing early signs of response¹⁰. Stop treatment only if there are no early signs of response.[1.8.2]*

12.2.7.3 *Continue alarm treatment in children with bedwetting who are showing signs of response until a minimum of 2 weeks' uninterrupted dry nights have been achieved [1.8.3].*

¹⁰ Early signs of a response may include smaller wet patches, waking to the alarm, the alarm going off later and fewer times per night and fewer wet nights.

- 12.2.7.4 *Assess whether it is appropriate to continue with alarm treatment if complete dryness is not achieved after 3 months. Only continue with alarm treatment if the child's bedwetting is still improving and the child and parents or carers are motivated to continue. [1.8.4]*
- 12.2.7.5 *Do not exclude alarm treatment as an option for bedwetting in children with:*
- *daytime symptoms as well as bedwetting*
 - *secondary bedwetting.[1.8.5]*
- 12.2.7.6 *Consider an alternative type of alarm (for example, a vibrating alarm) for the treatment of bedwetting in children who have a hearing impairment. [1.8.6]*
- 12.2.7.7 *Consider an alarm for the treatment of bedwetting in children with learning difficulties and/or physical disabilities. Tailor the type of alarm to each child's needs and abilities.[1.8.7]*
- 12.2.7.8 *Consider an alarm for the treatment of bedwetting in children under 7 years, depending on their ability, maturity, motivation and understanding of the alarm.[1.8.8]*
- 12.2.7.9 *Inform parents or carers about the benefits of alarms combined with reward systems. Advise them to use positive rewards for desired behaviour, such as waking up when the alarm goes off, going to the toilet after the alarm has gone off, returning to bed and resetting the alarm.[1.8.9]*
- 12.2.7.10 *Encourage children with bedwetting and their parents or carers to discuss and agree on their roles and responsibilities for using the alarm and the use of rewards [1.8.10]*

12.2.8 Supporting recommendations -evidence to recommendations

Economic considerations

No economic evidence was identified to support these recommendations, however the GDG felt that informing children and their parents/carers of the aims of treatment, how to use the device and how and when they might observe results may encourage adherence to a treatment that may produce only a gradual response. Additionally, offering children and their parents/carers advice on what to do if they experience a recurrence following success may reduce re-presentation at clinics.

Quality of evidence (this includes clinical and economic)

No evidence was identified.

Other considerations

The GDG considered that while alarms may have a sustained effect on dryness an alarm requires considerable effort and perseverance from both child and family, including siblings and extended family. The GDG considered that an important part of considering an alarm was assessing whether the child and family have the necessary motivation, time and energy to use an alarm. Contextual factors such as e.g. a new baby in the house might make an alarm a less attractive first line treatment. The GDG were particularly concerned that in situations where family members are already finding it difficult to cope with bedwetting and where parents or carers may be expressing anger to the child, the introduction of an alarm might result in a more punitive approach to the child.

The GDG considered it important that child and parents or carers were properly informed about how an alarm works and that it may take some weeks for it to have an effect. The GDG also discussed from clinical experience the importance of recording the time child waked and how wet they were as this can be a sign of commitment and allows for positive feedback during follow up clinics.

The GDG considered that the use of an alarm can be difficult for a child and parent or carers to master and that families may need considerable advice and support and access to expertise when starting to use an alarm. The GDG used their experience both as professional and patient members to develop recommendations around the likely information children and parents need when using an alarm. This covered how to use the alarm, what to expect, the signs of response and information about dealing with problems with the alarm and how to return it. Offering and agreeing appropriate support was considered by the GDG to be vital in helping families have confidence in their use of alarm.

12.2.9 Recommendations

- 12.2.9.1 *Explore and assess the ability of the family to cope with using an alarm for the treatment of bedwetting.[1.4.4]*
- 12.2.9.2 *Consider whether it is appropriate to offer alarm or drug treatment, depending on the age of the child, the frequency of bedwetting and the motivation and needs of the child and family.[1.4.5]*
- 12.2.9.3 *Ensure that advice and support are available to children and parents or carers who are given an alarm, and agree how these should be obtained.*

Be aware that they may need a considerable amount of help in learning how to use an alarm.[1.8.11]

12.2.9.4 *Inform the child and parents or carers that the aims of alarm treatment for bedwetting are to train the child to:*

- *recognise the need to pass urine*
- *wake to go to the toilet or hold on*
- *learn over time to hold on or to wake spontaneously and stop wetting the bed.[1.8.12]*

12.2.9.5 *Inform the child and parents or carers that:*

- *alarms have a high long-term success rate*
- *using an alarm can disrupt sleep*
- *that parents or carers may need to help the child to wake to the alarm*
- *using an alarm requires sustained parental and child commitment, involvement and effort*
- *they need to record their progress (for example, if and when the child wakes and how wet the child and bed are)*
- *alarms are not suitable for all children and families.[1.8.13]*

12.2.9.6 *If offering an alarm for bedwetting in children, inform the child and parents or carers how to:*

- *set and use the alarm*
- *respond to the alarm when it goes off*
- *maintain the alarm*
- *deal with problems with the alarm, including who to contact when there is a problem*
- *return the alarm when they no longer need it.[1.8.14]*

12.2.9.7 *Inform the child and parents or carers that it may take a few weeks for the early signs of a response to the alarm to occur and that these may include:*

- *smaller wet patches*
- *waking to the alarm*
- *the alarm going off later and fewer times per night*
- *fewer wet nights.[1.8.15]*

12.2.9.8 *Inform the child and parents or carers that dry nights may be a late sign of response to the alarm and may take weeks to achieve. [1.8.16]*

12.2.9.9 *Inform the parents or carers that they can restart using the alarm immediately, without consulting a health professional, if the child starts bedwetting again following response to alarm treatment[1.8.17]*

13 Desmopressin and the management of bedwetting

13.1 Introduction

What is it? Desmopressin is a synthetic analogue of the naturally occurring anti diuretic hormone (ADH).

How does it work? In most children levels of ADH rise overnight and prevent as much water being excreted by the kidneys as during the day. This causes urine to become concentrated in a smaller volume overnight which allows the majority of children to sleep through the night without needing to pass urine. In some children this mechanism is late to become established and they continue to produce large volumes of dilute urine overnight meaning a full bladder and either needing to get up to pass urine (nocturia – about 10% children at 7 years) or if they fail to wake, they will wet the bed or soak pull ups in large volumes. Desmopressin works by mimicking the action of ADH. It does not prevent the normal development of the child's own ADH excretion.

How is it given? Desmopressin is given as either a melt or a tablet. The nasal spray is no longer licensed for bedwetting owing to an increased incidence of side effects. Younger children often prefer the melt as it avoids needing to swallow tablets. Desmopressin in either form should be taken before bedtime. Children should restrict their fluid intake to sips only from an hour before taking the medicine to 8 hours afterwards to avoid the potential for fluid overload and hyponatraemia (low sodium levels in the blood) which could be a serious side effect.

Side effects and contraindications. Desmopressin is a safe medicine with few side effects. The main concern is the possibility of fluid overload and hyponatraemia but this has not been reported to happen if advice regarding fluid restriction has been followed. Other side effects are rare but can include headache, stomach ache and occasional emotional disturbance. These settle quickly on stopping the medicine. Desmopressin has very few interactions with other medicines. There is no evidence for any side effects if desmopressin is taken long term.

Desmopressin should be avoided in children who have fluid control problems such as in heart failure and should be carefully considered if children are likely to find difficulty complying with the fluid restriction requirements.

Desmopressin is pharmacologically active when given by intravenously, subcutaneously, oral or nasal routes. The duration of action differs little between routes but absorption does so different dosages are required for different routes..

For NE the nasal route (either via a rhinyle or by nasal spray) was the only route used for many years until desmopressin tablets were developed. More recently desmopressin lyophilosate (desmomelt R) has been licensed for oral use.

In 2007 nasal desmopressin was withdrawn as a treatment for NE because of a significantly higher incidence of symptomatic hyponatraemia than oral desmopressin. Although not currently licensed much of the evidence for use of desmopressin has come from studies using nasal desmopressin. We have therefore included studies using nasal desmopressin as a comparator and as an intervention. Although there have been few comparisons of nasal desmopressin with desmopressin by other routes they do appear to have similar effectiveness.

In the systematic review of the research the evidence of effectiveness for nasal, oral and melt administration are reported separately.

13.2 What is the clinical and cost effectiveness of desmopressin for children and young people under 19 years who have bedwetting?

13.2.1 Evidence review

13.2.1.1 Intranasal desmopressin compared to placebo

Two randomised control trials, compared intranasal desmopressin to placebo, **Muller (2001)**¹⁰⁸ and **Uygur (1997)**¹⁵².

Table 13-1: 20 micro grams intranasal desmopressin compared to placebo - Clinical summary of findings

Outcome	20 micro grams intranasal desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights in the last 2 weeks of treatment (no SDs)	73	75	-	not pooled	VERY LOW

13.2.1.2 Intranasal desmopressin compared to amitriptyline

One randomised control trial **Burke (1995)**¹⁹ compared 20 micro grams intranasal desmopressin to 25 mg or 50 mg amitriptyline.

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Table 13-2: Intranasal desmopressin compared to amitriptyline - Clinical summary of findings

Outcome	Intranasal desmopressin	Amitriptyline	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	1/17 (5.9%)	3/14 (21.4%)	RR 0.27 (0.03 to 2.36)	156 fewer per 1000 (from 208 fewer to 291 more)	MODERATE
Mean number of wet nights per week at end of treatment	17	14	-	MD 1.4 (0.12 to 2.68)	MODERATE
Mean number of wet nights per week at follow up	17	14	-	MD -0.1 (-1.87 to 1.67)	MODERATE
Number of children who dropped out by end of trial	3/17 (17.6%)	0/14 (0%)	RR 5.83 (0.33 to 104.22)	0 more per 1000 (from 0 fewer to 0 more)	LOW

13.2.1.3 *Intranasal desmopressin compared to imipramine*

One randomised **Vertucci (1997)**¹⁵⁸ controlled trial compared 30 mcg intranasal desmopressin to 0.9 mg/kg imipramine.

Table 13-3: Intranasal desmopressin compared to imipramine - Clinical summary of findings

Outcome	Intranasal desmopressin	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	25/29 (86.2%)	19/28 (67.9%)	RR 1.27 (0.95 to 1.7)	183 more per 1000 (from 34 fewer to 475 more)	VERY LOW
Mean number of wet nights per week after treatment (no sd)	29	28	-	not pooled	VERY LOW

13.2.1.4 *Tablet desmopressin compared to imipramine*

One randomised control trial **Lee (2005)**⁹⁰ compared 200 micrograms tablet desmopressin to 25 mg imipramine.

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Table 13-4 Tablet desmopressin compared to imipramine - Clinical summary of findings

Outcome	Tablet desmopressin	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who dropped out by end of trial	3/49 (6.1%)	7/48 (14.6%)	RR 0.42 (0.12 to 1.53)	85 fewer per 1000 (from 128 fewer to 77 more)	VERY LOW

Table 13-5: Tablet desmopressin compared to imipramine for children with night and day time wetting - Clinical summary of findings

Outcome	Tablet desmopressin	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who had 0-1 wet nights per month	9/26 (34.6%)	3/25 (12%)	RR 2.88 (0.88 to 9.44)	226 more per 1000 (from 14 fewer to 1000 more)	VERY LOW
Mean number of wet nights per week at end of treatment	26	25	-	MD -1.4 (-2.25 to -0.55)	VERY LOW

13.2.1.5 *Intranasal Desmopressin compared to intranasal desmopressin combined with amitriptyline*

One randomised control trial **Burke (1995)**¹⁹ compared 20 micro grams intranasal desmopressin to 20 micro grams intranasal desmopressin and amitriptyline.

Table 13 -6: Intranasal desmopressin compared to intranasal desmopressin and amitriptyline - Clinical summary of findings

Outcome	Intranasal desmopressin	Intranasal desmopressin and amitriptyline	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	1/17 (5.9%)	5/14 (35.7%)	RR 0.16 (0.02 to 1.25)	300 fewer per 1000 (from 350 fewer to 89 more)	MODERATE

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Mean number of wet nights per week at end of treatment	17	14	-	MD 1.4 (-0.14 to 2.94)	MODERATE
Mean number of wet nights per week at end of follow up	17	14	-	MD -1.3 (-3.2 to 0.6)	MODERATE
Number of children who dropped out by end of trial	3/17 (17.6%)	3/14 (21.4%)	RR 0.82 (0.2 to 3.46)	39 fewer per 1000 (from 171 fewer to 526 more)	MODERATE

13.2.1.6 *Tablet desmopressin compared to tablet desmopressin with oxybutynin*

One randomised control trial **Lee (2005)**⁹⁰ compared 200 microgram tablet desmopressin to 100 to 200 microgram tablet desmopressin and 5 mg oxybutynin.

Table 13-7: Tablet desmopressin compared to tablet desmopressin and oxybutynin - Clinical summary of findings

Outcome	Tablet desmopressin	Tablet desmopressin and oxybutynin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who dropped out by end of trial	3/49 (6.1%)	3/48 (6.3%)	RR 0.98 (0.21 to 4.62)	1 fewer per 1000 (from 50 fewer to 228 more)	VERY LOW

Table 13-8: Tablet desmopressin compared to tablet desmopressin and oxybutynin for children with night and day wetting - Clinical summary of findings

Outcome	Tablet desmopressin	Tablet desmopressin and oxybutynin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who had 0-1 wet nights per month	9/26 (34.6%)	9/26 (34.6%)	RR 1 (0.47 to 2.11)	0 fewer per 1000 (from 183 fewer to 384 more)	VERY LOW
Mean number of wet nights per week at end of treatment	26	26	-	MD 0.03 (-0.66 to 0.72)	VERY LOW

13.2.1.7 *Tablet desmopressin compared to placebo for children with bed wetting*

Three randomised control trials, **Ferrara (2008)**⁵⁵, **Schulman (2001)**¹³⁶ and **Skoog (1997)**¹³⁹ compared tablet desmopressin to placebo. **Ferrara (2008)**⁵⁵ was identified in the update search, all three trials considered children who had only night time wetting.

Table13 -9: 200 microgram tablet desmopressin compared to placebo - Clinical summary of findings

Outcome	200 microgram tablet desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	29/127 (22.8%)	0/135 (0%)	RR 10.96 (1.6 to 75.16)	0 more per 1000 (from 0 more to 0 more)	LOW
Mean number of wet nights per 2 weeks at end of treatment	33	36	-	MD -1 (-1.55 to -0.45)	LOW

Table 13- 10: 400 microgram tablet desmopressin compared to placebo - Clinical summary of findings

Outcome	400 microgram tablet desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	10/81 (12.3%)	0/85 (0%)	RR 11.42 (1.5 to 86.69)	0 more per 1000 (from 0 more to 0 more)	MODERATE
Mean number of wet nights per 2 weeks at end of treatment	35	36	-	MD -1.5 (-2.12 to -0.88)	MODERATE

Table 13-11: 600 microgram tablet desmopressin compared to placebo - Clinical summary of findings

Outcome	600 microgram tablet desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	5/82 (6.1%)	0/85 (0%)	RR 6.19 (0.76 to 50.48)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Mean number of wet nights per 2 weeks at end of treatment	33	36	-	MD -1.5 (-2.05 to -0.95)	MODERATE

13.2.1.8 Low dose tablet desmopressin compared to high dose tablet desmopressin for children with bedwetting

Two randomised control trials **Schulman (2001)**¹³⁶ and **Skoog (1997)**¹³⁹ compared low dose tablet desmopressin to high dose tablet desmopressin. Both trials considered children who had bedwetting. **Skoog (1997)**¹³⁹ excluded children who were previously non responsive (less than 50% reduction in the number of wet nights) to desmopressin for the study.

Table 13 -12: 200 microgram tablet desmopressin compared to 400 microgram tablet desmopressin - Clinical summary of findings

Outcome	200 microgram tablet desmopressin	400 microgram tablet desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	3/77 (3.9%)	10/81 (12.3%)	RR 0.32 (0.09 to 1.12)	84 fewer per 1000 (from 112 fewer to 15 more)	LOW
Mean number of wet nights in last 2 weeks of treatment	28	28	-	MD 0.5 (-0.24 to 1.24)	LOW

Table 13-13: 200 microgram tablet desmopressin compared to 600 microgram tablet desmopressin - Clinical summary of findings

Outcome	200 microgram tablet desmopressin	600 micrograms tablet desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	3/77 (3.9%)	5/82 (6.1%)	RR 0.65 (0.16 to 2.62)	21 fewer per 1000 (from 51 fewer to 99 more)	LOW

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Mean number of wet nights in last 2 weeks of treatment	28	28	-	MD 0.04 (-0.94 to 1.01)	LOW
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Table 13 -14: 400 microgram tablet desmopressin compared to 600 microgram tablet desmopressin - Clinical summary of findings

Outcome	400 microgram tablet desmopressin	600 microgram tablet desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	10/81 (12.3%)	5/82 (6.1%)	RR 2.02 (0.72 to 5.66)	62 more per 1000 (from 17 fewer to 284 more)	LOW
Mean number of wet nights in last 2 weeks of treatment	28	28	-	MD -0.45 (-1.42 to 0.53)	LOW

13.2.1.9 Tablet desmopressin compared to melt desmopressin for children with bedwetting

One randomised control trial **Lottmann (2007)**⁹³ compared 200 or 2 X 200 microgram tablet desmopressin to 120 or 240 micro grams melt desmopressin. **Lottmann (2007)**⁹³ considered children who had bedwetting. The study was an equivalence study.

Table 13-15: Tablet desmopressin compared to melt desmopressin - Clinical summary of findings

Outcome	Tablet desmopressin	Melt desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week	112	112	-	MD -0.02 (-0.52 to 0.48)	VERY LOW

13.2.1.10 Intranasal desmopressin compared to enuresis alarms for children with bedwetting

One randomised control trial **Wille (1986)**¹⁶⁷ compared 200 micro grams intranasal desmopressin to enuresis alarms. **Wille (1986)**¹⁶⁷ considered children who had only bedwetting.

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Table 13-16: Intranasal desmopressin compared to enuresis alarm for children with bedwetting - Clinical summary of findings

Outcome	Intranasal desmopressin	Enuresis alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 5 wet nights in 28 nights	17/24 (70.8%)	19/22 (86.4%)	RR 0.82 (0.6 to 1.11)	156 fewer per 1000 (from 346 fewer to 95 more)	VERY LOW
Mean number of wet nights per week at end of treatment	24	22	-	MD 1 (-0.11 to 2.11)	VERY LOW
Number of children who dropped out by end of trial	10/24 (41.7%)	1/22 (4.5%)	RR 9.17 (1.28 to 65.9)	368 more per 1000 (from 13 more to 1000 more)	VERY LOW

13.2.1.11 Tablet desmopressin compared to enuresis alarms for children with bedwetting

One randomised control trial **Ng (2005)**¹¹⁵ compared 200 microgram tablet desmopressin to enuresis alarms. **Ng (2005)**¹¹⁵ considered children who had bedwetting.

Table 13-17 Tablet desmopressin compared to enuresis alarm - Clinical summary of findings

Outcome	Tablet desmopressin	Enuresis alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	16/38 (42.1%)	8/35 (22.9%)	RR 1.84 (0.9 to 3.76)	192 more per 1000 (from 23 fewer to 632 more)	LOW
Mean number of wet nights per week at end of treatment	36	28	-	MD -0.1 (-1.23 to 1.03)	LOW
Number of children who relapsed at 3 months	9/16 (56.3%)	0/8 (0%)	RR 10.06 (0.66 to 153.71)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children who dropped out at end of trial	2/38 (5.3%)	7/35 (20%)	RR 0.26 (0.06 to 1.18)	148 fewer per 1000 (from 188 fewer to 36 more)	LOW

13.2.1.12 *All desmopressin compared to enuresis alarms for children with bedwetting*

Two randomised control trials **Ng (2005)**¹¹⁵ and **Wille (1986)**¹⁶⁷ compared desmopressin (intranasal desmopressin or tablet desmopressin) to enuresis alarms. Both studies considered children who had only bedwetting. See GRADE table in Evidence review Alarms – Section 12.2.1

13.2.1.13 *Tablet desmopressin compared to imipramine for children with bedwetting*

One randomised control trial **Lee (2005)**⁹⁰ compared 200 microgram tablet desmopressin to 25 mg imipramine for children with bedwetting.

Table 13 -18: Tablet desmopressin compared to imipramine for children with bedwetting - Clinical summary of findings

Outcome	Tablet desmopressin	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who had 0-1 wet nights per month	14/23 (60.9%)	3/23 (13%)	RR 4.67 (1.55 to 14.09)	477 more per 1000 (from 71 more to 1000 more)	LOW
Mean number of wet nights per week at end of treatment	23	23	-	MD -1.3 (-2.22 to -0.38)	VERY LOW

13.2.1.14 *Tablet desmopressin compared to tablet desmopressin combined with enuresis alarms for children with bedwetting*

One randomised control trial **Ng (2005)**¹¹⁵ compared 200 micro grams tablet desmopressin to 200 micro grams tablet desmopressin with enuresis alarms.

Table 13-19: Tablet desmopressin compared to tablet desmopressin and enuresis alarm for children with bedwetting - Clinical summary of findings

Outcome	Tablet desmopressin	Tablet desmopressin and enuresis alarm	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	16/38 (42.1%)	20/32 (62.5%)	RR 0.67 (0.43 to 1.07)	206 fewer per 1000 (from 356 fewer to 44 more)	LOW
Mean number of wet nights per week at end of treatment	36	29	-	MD 1.4 (0.35 to 2.45)	LOW
Number of children who relapsed at 3 months	9/16 (56.3%)	7/20 (35%)	RR 1.61 (0.77 to 3.36)	214 more per 1000 (from 81 fewer to 826 more)	LOW
Number of children who dropped out by end of trial	2/38 (5.3%)	3/32 (9.4%)	RR 0.56 (0.1 to 3.15)	41 fewer per 1000 (from 85 fewer to 202 more)	LOW

13.2.1.15 *Tablet desmopressin compared to tablet desmopressin with oxybutynin for children with bedwetting*

One randomised control trial **Lee (2005)**⁹⁰ compared 200 microgram tablet desmopressin to 100 to 200 microgram tablet desmopressin and 5 mg oxybutynin for children with bedwetting.

Table 13-20: Tablet desmopressin compared to tablet desmopressin and oxybutynin for children with bedwetting - Clinical summary of findings

Outcome	Tablet desmopressin	Tablet desmopressin and oxybutynin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who had 0-1 wet nights per month	14/23 (60.9%)	14/22 (63.6%)	RR 0.96 (0.61 to 1.51)	25 fewer per 1000 (from 248 fewer to 324 more)	VERY LOW
Mean number of wet nights per week at end of treatment	23	22	-	MD -0.23 (-0.91 to 0.45)	VERY LOW

13.2.1.16 *Intranasal desmopressin compared to placebo for children with monosymptomatic nocturnal enuresis*

Two randomised control trials, **Longstaffe (2000)**⁹² and **Rushton (1995)**¹³², compared intranasal desmopressin placebo for children with monosymptomatic nocturnal enuresis.

Table 13-21: 20 micro grams intranasal desmopressin compared to placebo for children with monosymptomatic nocturnal enuresis - Clinical summary of findings

Outcome	20 micro grams intranasal desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	39/109 (35.8%)	24/108 (22.2%)	RR 2.83 (0.35 to 22.68)	406 more per 1000 (from 144 fewer to 1000 more)	VERY LOW
Mean number of wet nights in last 2 weeks of treatment	49	47	-	MD -1.88 (-3.51 to -0.25)	VERY LOW
Number of children who dropped out by end of trial	5/60 (8.3%)	4/61 (6.6%)	RR 1.27 (0.36 to 4.51)	18 more per 1000 (from 42 fewer to 232 more)	LOW

Table 13- 22: 40 micro grams intranasal desmopressin compared to placebo for children with monosymptomatic nocturnal enuresis - Clinical summary of findings

Outcome	40 micro grams intranasal desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	10/49 (20.4%)	1/47 (2.1%)	RR 9.59 (1.28 to 72.04)	180 more per 1000 (from 6 more to 1000 more)	LOW
Mean number of wet nights per week at end of treatment	49	47	-	MD -2.25 (-4 to -0.5)	VERY LOW

13.2.1.17 Tablet desmopressin compared to placebo for children with monosymptomatic nocturnal enuresis

One randomised control trial, **Yap (1998)**¹⁶⁹ compared tablet desmopressin to placebo.

Table 13-23: 400 microgram tablet desmopressin compared to placebo for children with monosymptomatic nocturnal enuresis - Clinical summary of findings

Outcome	400 microgram tablet desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	23/34 (67.6%)	7/34 (20.6%)	RR 3.29 (1.63 to 6.62)	472 more per 1000 (from 130 more to 1000 more)	MODERATE
Mean number of wet nights per 2 weeks at end of treatment	34	34	-	MD -2 (-3.15 to -0.85)	LOW

13.2.1.18 Intranasal desmopressin compared to enuresis alarms for children with monosymptomatic nocturnal enuresis

One randomised control trial **Longstaffe (2000)**⁹² compared 200 micro grams intranasal desmopressin to enuresis alarms.

Table 13- 24: Intranasal desmopressin compared to enuresis alarm for children with monosymptomatic nocturnal enuresis - Clinical summary of findings

Outcome	Intranasal desmopressin	Enuresis alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	29/60 (48.3%)	35/61 (57.4%)	RR 0.84 (0.6 to 1.18)	92 fewer per 1000 (from 230 fewer to 103 more)	LOW
Number of children who dropped out by end of trial	5/60 (8.3%)	8/61 (13.1%)	RR 0.64 (0.22 to 1.83)	47 fewer per 1000 (from 102 fewer to 109 more)	LOW

13.2.1.19 Desmopressin compared to enuresis alarms for children with bedwetting

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One randomised control trial **Tuygun (2007)**¹⁵¹ compared desmopressin (20 to 40 micro grams intranasal desmopressin or 200 to 300 microgram tablet desmopressin) to enuresis alarms.

Table 13 -25: Desmopressin compared to enuresis alarm - Clinical summary of findings

Outcome	Desmopressin	Enuresis alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	25/49 (51%)	20/35 (57.1%)	RR 0.89 (0.6 to 1.33)	63 fewer per 1000 (from 228 fewer to 188 more)	LOW
50-90% reduction in the number of wet nights at end of treatment	15/49 (30.6%)	9/35 (25.7%)	RR 1.19 (0.59 to 2.41)	49 more per 1000 (from 105 fewer to 362 more)	LOW
Mean number of wet nights per month at end of treatment	49	19	-	MD 7.29 (2.67 to 11.91)	LOW
Number of children who relapsed at 6 months	27/49 (55.1%)	10/35 (28.6%)	RR 1.93 (1.08 to 3.45)	266 more per 1000 (from 23 more to 701 more)	LOW

13.2.1.20 All desmopressin compared to enuresis alarms for children with monosymptomatic children

Two randomised control trials **Longstaffe (2000)**⁹² and **Tuygun (2007)**¹⁵¹ compared desmopressin (intranasal desmopressin or tablet desmopressin) to enuresis alarms.

Table 13-26: All desmopressin compared to enuresis alarm for children with monosymptomatic nocturnal enuresis - Clinical summary of findings

Outcome	Desmopressin	Enuresis alarm	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	54/109 (49.5%)	49/96 (51%)	RR 0.96 (0.73 to 1.25)	20 fewer per 1000 (from 138 fewer to 128 more)	LOW
50-90% reduction in the number of wet nights at end of treatment	15/49 (30.6%)	9/35 (25.7%)	RR 1.19 (0.59 to 2.41)	49 more per 1000 (from 105 fewer to 362 more)	LOW
Mean number of wet nights per month at end of treatment	49	19	-	MD 7.29 (2.67 to 11.91)	LOW
Number of children who relapsed at 6 months	27/49 (55.1%)	10/35 (28.6%)	RR 1.93 (1.08 to 3.45)	266 more per 1000 (from 23 more to 701 more)	LOW
Number of children who dropped out	5/60 (8.3%)	8/61 (13.1%)	RR 0.64 (0.22 to 1.83)	47 fewer per 1000 (from 102 fewer to 109 more)	LOW

13.2.1.21 *Intranasal desmopressin compared to placebo for young children*

One randomised controlled trial **Birkasova (1978)**¹³, compared intranasal desmopressin to placebo for young children.

Table 13-27: 10 micro grams intranasal desmopressin compared to placebo - Clinical summary of findings

Outcome	10 micro grams intranasal desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	0/22 (0%)	0/22 (0%)	not pooled	not pooled	LOW
Mean number of wet nights per 2 weeks at end of treatment	22	22	-	MD -6.8 (-9.43 to -4.17)	LOW

Table 13-28: 40 micro grams intranasal desmopressin compared to placebo for young children - Clinical summary of findings

Outcome	40 micro grams intranasal desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	5/22 (22.7%)	0/22 (0%)	RR 11 (0.64 to 187.67)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Mean number of wet nights in the last 2 weeks of treatment	22	22	-	MD -6.8 (-9.43 to -4.17)	LOW

13.2.1.22 Low dose intranasal desmopressin compared to high dose intranasal desmopressin for young children

One randomised control trial **Birkasova (1978)**¹³ compared low dose intranasal desmopressin to high dose intranasal desmopressin for young children.

Table 13- 29: 10 micro grams intranasal desmopressin compared to 40 micro grams intranasal desmopressin - Clinical summary of findings

Outcome	10 micro grams intranasal desmopressin	40 micro grams intranasal desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	0/22 (0%)	5/22 (22.7%)	RR 0.09 (0.01 to 1.55)	207 fewer per 1000 (from 225 fewer to 125 more)	VERY LOW

13.2.1.23 Side effects of desmopressin compared to placebo for children with bedwetting

Two randomised controlled trials, **Schulman (2001)**¹³⁶ and **Skoog (1997)**¹³⁹, compared desmopressin to placebo.

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Table 13 -30: Side effects of tablet desmopressin compared to placebo - Clinical summary of findings

Outcome	Desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children with vomiting causing withdrawal	2/109 (1.8%)	0/38 (0%)	RR 1.77 (0.09 to 36.12)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Number of children with rhinitis, pharyngitis, infection, headache or fever	43/143 (30.1%)	13/48 (27.1%)	RR 1.11 (0.66 to 1.88)	30 more per 1000 (from 92 fewer to 238 more)	LOW
Number of children who only required 400 microgram desmopressin	3/99 (3%)	0/38 (0%)	RR 9.75 (0.59 to 160.72)	0 more per 1000 (from 0 fewer to 0 more)	LOW

13.2.1.24 Desmopressin compared to placebo for children with monosymptomatic nocturnal enuresis

Ne randomised controlled trial, **Lottmann (2007)**⁹³, considered side effects of using desmopressin for children with monosymptomatic nocturnal enuresis.

Table 13 -31: Side effects of tablet desmopressin compared to melt desmopressin - Clinical summary of findings

Outcome	Melt desmopressin	Tablet desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children with headaches	6/109 (5.5%)	0/109 (0%)	RR 13 (0.74 to 227.97)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children with diarrhoea	3/109 (2.8%)	0/109 (0%)	RR 7 (0.37 to 133.93)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children with viral gastroenteritis	3/109 (2.8%)	0/109 (0%)	RR 7 (0.37 to 133.93)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

13.2.2 Network Meta-Analysis

Desmopressin was amongst the interventions included in a network meta-analysis of interventions used for nocturnal enuresis. The summary of results of this analysis is presented in chapter 24 and a detailed description of the analysis is presented in appendix F. If studies did not meet the inclusion criteria of the network meta-analysis protocol as stated in appendix F they were not included in the network meta-analysis

13.2.3 Health economic evidence review

Given the lack of published evidence assessing the cost-effectiveness of different interventions, including desmopressin, used in the treatment of bedwetting, the GDG identified this area as high priority for original economic analysis. Therefore, a cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK National Health Service and Personal Social Services perspective. The time horizon for the analysis was 13 years, modelling patients from the time they entered at age 7 years until they reached age 20.

A summary of the analysis is provided below. The full report is presented in appendix G.

Summary of results

The results of the probabilistic sensitivity analysis are summarised in table 13-32 in terms of mean total costs and mean total QALYs and mean net benefit for each treatment sequence, where each mean is the average of 20,000 simulated estimates. The option with the greatest mean net benefit is the most cost-effective at a specified threshold (for example, £20,000). The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

Table 13-32: Basecase probabilistic sensitivity analysis results

Treatment sequence	Mean cost	Mean QALYs	Net Benefit (threshold=£20,000 per QALY)	Probability that strategy is most cost-effective (threshold =£20,000 per QALY)
No Treatment	£0	19.734	£394,684	0.0%
Alarm - Imipramine	£206	19.901	£397,816	0.4%
Imipramine - Desmopressin	£406	19.914	£397,875	0.0%
Imipramine - Desmopressin - Desmopressin+Anticholinergic	£514	19.922	£397,929	0.0%

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Desmopressin - Imipramine	£298	19.912	£397,943	0.7%
Imipramine - Alarm - Desmopressin	£374	19.927	£398,169	0.0%
Imipramine - Alarm - Desmopressin - Desmopressin+Anticholinergic	£434	19.932	£398,203	0.0%
Desmopressin - Alarm - Imipramine	£304	19.952	£398,729	0.3%
Alarm - Desmopressin - Imipramine	£275	19.955	£398,814	0.1%
Alarm - Imipramine - Desmopressin	£310	19.959	£398,877	0.0%
Alarm - Imipramine - Desmopressin - Desmopressin+Anticholinergic	£367	19.964	£398,910	0.0%
Desmopressin - Alarm+Desmopressin - Imipramine	£378	19.978	£399,178	3.1%
Desmopressin	£314	19.981	£399,297	7.1%
Alarm - Alarm+Desmopressin - Imipramine	£252	19.981	£399,357	13.1%
Desmopressin - Desmopressin+Anticholinergic	£426	19.990	£399,370	19.8%
Alarm - Desmopressin	£280	19.991	£399,549	4.9%
Desmopressin - Alarm+Desmopressin - Desmopressin	£410	19.998	£399,551	3.3%
Alarm - Desmopressin - Desmopressin+Anticholinergic	£346	19.997	£399,592	5.6%
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£433	20.002	£399,603	3.9%
Desmopressin - Alarm - Desmopressin	£350	19.998	£399,609	7.7%
Alarm - Alarm+Desmopressin - Desmo	£258	19.995	£399,640	15.9%
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£281	19.996	£399,647	8.3%
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£373	20.001	£399,647	5.8%

The results of the incremental analysis in the probabilistic analysis, excluding dominated and extendedly dominated strategies, are presented in table 13-33.

Table 13-33: Incremental analysis of basecase probabilistic results with dominated and extendedly dominated sequences removed

Treatment sequence	Mean cost (£)	Incremental Cost (£)	Mean QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		19.73421		
Alarm - Alarm+Desmopressin - Desmo	£258	£258	19.99489	0.26068	£988
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£282	£24	19.9964	0.00151	£15,828
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£373	£91	20.00099	0.00459	£19,891
Desmopressin - Alarm+Desmopressin - Desmopressin /	£433	£61	20.00183	0.00084	£72,143

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The GDG considered that the differences between intervention sequences were relatively small and the probabilistic results indicated substantial uncertainty around the mean cost and benefit estimates. Small changes to the model inputs appears to result in substantial changes to the conclusions about modelled sequences' relative and overall cost-effectiveness.

The GDG was concerned that alarms, despite their cost-effectiveness, may not be an appropriate intervention for all children. For this group of children, a strategy of starting and maintaining desmopressin with or without the addition of an anticholinergic until sustained dryness is achieved is considered cost-effective.

A series of sensitivity analyses were undertaken to test some of the assumptions feeding into the model and none of these affected the cost-effectiveness of the sequence alarm followed by combined alarm and desmopressin and then desmopressin alone compared to no treatment. However, there was some substantial variation in the relative cost-effectiveness of sequences commencing with initial desmopressin.

If the assumption is made that bedwetting is bedwetting and dry is dry, then a partial response to ongoing treatment is no better than no response and a full response to ongoing treatment is the same as a sustained response off treatment. In this scenario, a treatment sequence of desmopressin followed by alarm and then by desmopressin or combined desmopressin and anticholinergic is very likely to be cost-effective. Without real data to inform the utilities of these different health states, it is difficult to know whether this scenario or the basecase scenario is a better reflection of reality.

The basecase analysis included the potential quality of life gain for parents and carers if their child were to achieve temporary or sustained dryness. In a sensitivity analysis, these health benefits were excluded to assess the cost-effectiveness of intervention sequences if there was no health gain accrued to parents and carers. In this scenario, no strategies starting with desmopressin were cost-effective.

In the basecase, treatment only commenced for hypothetical patients at the age of 7 years. In actuality, some children may seek treatment starting at the age of 5 years. When the model is rerun from the age of 5 years, the same treatment sequences as in the base case are included in the incremental analysis, however the ICERs for all strategies except for alarm followed by combined alarm and desmopressin and then desmopressin alone are greater than £20,000 per QALY gained and therefore unlikely to be cost-effective. Treatment sequences starting at age 5 with initial

desmopressin are only cost-effective if alarm-based strategies are unsuitable and therefore removed from the list of comparators.

In the basecase it was assumed that 100% of children who experienced a recurrence of bedwetting within 1 week of discontinuing treatment following a full response would resume treatment, either with the same intervention that had worked before or with the next intervention in the sequence. In a sensitivity analysis, this assumption was relaxed to 50% and 75% and results showed that sequences commencing with desmopressin were not cost-effective.

The economic analysis conducted and presented here represents the first undertaken to assess the cost-effectiveness of interventions used in the treatment of children with bedwetting. And although the analysis is directly applicable to decision making in the UK NHS, it has some potentially serious limitations, some of which may significantly impact the overall conclusions that can be drawn. The main limitations of the analysis are related to the fact that assumptions had to be made in the absence of evidence. Some of these key assumptions centre around:

- treatment effectiveness being independent of age
- health care resource use having been estimated by GDG
- utility weights having been estimated by GDG

A full discussion of these can be found in appendix G.

13.2.4 Evidence statements

The evidence statements are presented according to population in each study and the method of administration of desmopressin.

Studies included children with bedwetting and possible day time symptoms

Intranasal desmopressin

Muller (2001)¹⁰⁸, Uygur (1997)¹⁵²

- Two studies showed that children treated with 20 micro grams intranasal desmopressin had 1.63 to 8.6 fewer wet nights in the last 2 weeks of treatment compared to those who were treated with placebo. Children had a mean age of 8.6 to 8.7 in Muller (2001) and an age range of 7 to 17 in Uygur (1997); treatment length was 2 weeks to 6 months. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Burke (1995)¹⁹

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with intranasal desmopressin and those treated with amitriptyline. Relative risk 0.27, 95% CI 0.03, 2.36. Children had an age range of 8.6 to 8.9 years and treatment was for 16 weeks.
- Patients treated with amitriptyline had fewer wet nights per week at the end of treatment than those treated with intranasal desmopressin. Mean difference 1.4, 95% CI 0.12, 2.68. Children had an age range of 8.6 to 8.9 years and treatment was for 16 weeks.
- One study showed there was no statistically significant difference in the number of wet nights per week at follow up between children treated with intranasal desmopressin and those treated with amitriptyline. Mean difference -0.1, 95% CI -1.87, 1.67. Children had an age range of 8.6 to 8.9 years and treatment was for 16 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out of the trial between the children treated with intranasal desmopressin and those treated with amitriptyline. Relative risk 5.83, 95% CI 0.33, 104.22. Children had an age range of 8.6 to 8.9 years and treatment was for 16 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with intranasal desmopressin and those treated with intranasal desmopressin and amitriptyline. Relative risk 0.16, 95% CI 0.02, 1.25. Children had an age range of 8.6 to 8.9 years and treatment was for 16 weeks.
- One study showed there was no statistically significant difference in the number of wet nights per week at the end of treatment between children treated with intranasal desmopressin and those treated with intranasal desmopressin and amitriptyline. Mean difference 1.4, 95% CI -0.14, 2.94. Children had an age range of 8.6 to 8.9 years and treatment was for 16 weeks.
- One study showed there was no statistically significant difference in the number of wet nights per week at follow up between children treated with intranasal desmopressin and those treated with intranasal desmopressin and amitriptyline. Mean difference -1.3, 95% CI -3.2, 0.6. Children had an age range of 8.6 to 8.9 years and treatment was for 16 weeks.

- One study showed there was no statistically significant difference in the number of children who dropped out of the trial between the children treated with intranasal desmopressin and those treated with intranasal desmopressin and amitriptyline. Relative risk 0.82, 95% CI 0.2, 3.46. Children had an age range of 8.6 to 8.9 years and treatment was for 16 weeks.

Vertucci (1997) ¹⁵⁸

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with intranasal desmopressin and those treated with imipramine. Relative risk 1.27, 95% CI 0.95, 1.70. Children had an age range of 6 to 15 years and treatment was for 3 weeks.
- One study showed children treated with intranasal desmopressin had 1.5 fewer wet nights per week at the end of treatment compared to children treated with imipramine. Children had an age range of 6 to 15 years and treatment was for 3 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable

Tablet desmopressin

Lee (2005) ⁹⁰

- One study showed there was no statistically significant difference in the number of children who achieved 0 to 1 wet nights per month between the children treated with tablet desmopressin and those treated with imipramine. Relative risk 2.88, 95% CI 0.88, 9.44. Children had a mean age of 7.8 years and treatment was for 6 months.
- One study showed children treated with tablet desmopressin had fewer wet nights per week at end of treatment compared to those treated with imipramine. Mean difference -1.4, 95% CI -2.25, -0.55. Children had a mean age of 7.8 years and treatment was for 6 months.
- One study showed there was no statistically significant difference in the number of children who dropped out between the children treated with tablet desmopressin and those treated with imipramine. Relative risk 0.42, 95% CI 0.12, 1.53. Children had a mean age of 7.8 years and treatment was for 6 months.

- One study showed children continue to have a decrease in the number of wet nights at 1 month, 3 months and 6 months in treatment with both desmopressin or imipramine treatment. Children had a mean age of 7.8 years and were treated for 6 months.
- One study showed there was no difference in the number of children who achieved 0 to 1 wet nights per month between the children treated with tablet desmopressin and those treated with tablet desmopressin and oxybutynin. Relative risk 1, 95% CI 0.47, 2.11. Children had a mean age of 7.8 years and treatment was for 6 months.
- One study showed there was no statistically significant difference in the number of wet nights per week at follow up between children treated with tablet desmopressin and those treated with tablet desmopressin and oxybutynin. Mean difference 0.03, 95% CI -0.66, 0.72. Children had a mean age of 7.8 years and treatment was for 6 months.
- One study showed there was no statistically significant difference in the number of children who dropped out between the children treated with tablet desmopressin and those treated with tablet desmopressin and oxybutynin. Relative risk 0.98 95% CI 0.21, 4.62. Children had a mean age of 7.8 years and treatment was for 6 months.
- One study showed children continue to have a decrease in the number of wet nights at 1 month, 3 months and 6 months in treatment with either desmopressin or desmopressin combined with oxybutynin treatment. Children had a mean age of 7.8 years and were treated for 6 months.

Studies include children with bedwetting only

Intranasal desmopressin

Wille (1986)¹⁶⁷

- Two studies showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with intranasal desmopressin and those treated enuresis alarms. Relative risk 0.82, 95% CI 0.6, 1.11. Children were aged over 6 years and treatment was for 3 months.
- One study showed there was no statistically significant difference in the number of wet nights per week at the end of treatment between children treated with intranasal desmopressin and those treated with enuresis alarms.

Mean difference 1, 95% CI -0.11, 2.11. Children were aged over 6 years and treatment length was 3 months.

- One study showed that children treated with intranasal desmopressin had a faster response compared to children treated with an enuresis alarm. However after treatment children treated with an enuresis alarm had a continued higher response compared to children treated with desmopressin. Wille (1986) considered a response to be the number of dry nights. Children were aged over 6 years and treatment was for 3 months.
- One study showed children treated with intranasal desmopressin were more likely to drop out of the trial compared to children treated with enuresis alarms. Relative risk 9.17, 95% CI 1.28, 65.9. Children were aged over 6 years and treatment was for 3 months.

Tablet desmopressin

Ferrara (2008)⁵⁵, **Schulman (2001)**¹³⁶, **Skoog (1997)**¹³⁹

- Three studies showed children treated with 200 microgram tablet desmopressin were more likely to achieve 14 consecutive dry nights than those treated with placebo. Relative risk 10.96, 95% CI 1.6, 75.16. Children had a mean age of 8.5 to 11 years and treatment length was 2 weeks to 3 months.

Schulman (2001)¹³⁶, **Skoog (1997)**¹³⁹

- Two studies showed children treated with 400 microgram tablet desmopressin were more likely to achieve 14 consecutive dry nights than those treated with placebo. Relative risk 11.42, 95% CI 1.5, 86.69. Children had an age range of 4 to 18 and treatment length was 2 to 6 weeks.
- Two studies showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with 600 microgram tablet desmopressin and those treated with placebo. Relative risk 6.19, 95% CI 0.76, 50.48. Children had a mean age of 9.1 to 11 and treatment length was 2 to 6 weeks.

Skoog (1997)¹³⁹

- One study showed that children treated with 200 microgram tablet desmopressin had fewer wet nights per 2 weeks at the end of treatment

compared to those who were treated with placebo. Mean difference -1, 95% CI -1.55, -0.45. Children had a mean age of 9.1 to 9.5 years and treatment length was 6 weeks.

- One study showed that children treated with 400 microgram tablet desmopressin had fewer wet nights per 2 weeks at the end of treatment compared to those who were treated with placebo. Mean difference -1.5, 95% CI -2.12, -0.88. Children had a mean age 9.1 to 9.5 years and treatment length was 6 weeks.
- One study showed that children treated with 600 microgram tablet desmopressin had fewer wet nights per 2 weeks at the end of treatment compared to those who were treated with placebo. Mean difference -1.5, 95% CI -2.05, -0.95. Children had a mean age of 9.1 to 9.5 years and treatment length was 6 weeks.

Ng (2005)¹¹⁵

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with tablet desmopressin and those treated with enuresis alarms. Relative risk 1.84, 95% CI 0.9, 3.76. Children had a mean age of 9.5 years and treatment length was 3 months.
- One study showed there was no statistically significant difference in the number of wet nights per week at the end of treatment between children treated with tablet desmopressin and those treated with enuresis alarms. Mean difference -0.1, 95% CI -1.23, 1.03. Children had a mean age of 9.5 years and treatment length was 3 months.
- One study showed that children treated with an enuresis alarm had a faster response and continued response compared to children treated with tablet desmopressin. Ng (2005) considered a response to be a reduction in the number of wet nights. Children had a mean age of 9.5 years and treatment was for 3 months.
- One study showed there was no statistically significant difference in the number of children who relapsed at 3 months between the children treated with tablet desmopressin and those treated with enuresis alarms. Relative risk 10.06 95% CI 0.66, 153.71. Children had a mean age of 9.5 years and treatment length was 3 months.

- One study showed there was no statistically significant difference in the number of children who dropped out of the trial between the children treated with tablet desmopressin and those treated with enuresis alarms. Relative risk 0.26, 95% CI 0.06, 1.18. Children had a mean age of 9.5 years and treatment length was 3 months.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with tablet desmopressin and those treated with tablet desmopressin and enuresis alarms. Relative risk 0.67, 95% CI 0.43, 1.07. Children had a mean age of 9.5 years and treatment was for 12 weeks.
- Patients treated with tablet desmopressin and enuresis alarms had fewer wet nights per week at the end of treatment than those treated with tablet desmopressin. Mean difference 1.4, 95% CI 0.35, 2.45. Children had a mean age of 9.5 years and treatment was for 12 weeks.
- One study showed that children treated with tablet desmopressin and enuresis alarm had a faster response and continued response compared to children treated with desmopressin. Ng (2005) considered a response to be a reduction in the number of wet nights. Children had a mean age of 9.5 years and treatment was for 3 months.
- One study showed there was no statistically significant difference in the number of children who relapsed at 3 months between the children treated with tablet desmopressin and those treated with tablet desmopressin and enuresis alarms. Relative risk 1.61, 95% CI 0.77, 3.36. Children had a mean age of 9.5 years and treatment was for 12 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out between the children treated with tablet desmopressin and those treated with tablet desmopressin and enuresis alarms. Relative risk 0.56, 95% CI 0.1, 3.15. Children had a mean age of 9.5 years and treatment was for 12 weeks.

Lee (2005)⁹⁰

- One study showed more children treated with tablet desmopressin achieved 0 to 1 wet nights per month than children treated with imipramine. Relative risk 4.67, 95% CI 1.55, 14.09. Children had a mean age of 7.8 years and treatment was for 6 months.

- Patients treated with tablet desmopressin had fewer wet nights per week at the end of treatment than those treated with imipramine. Mean difference -1.3, 95% CI -2.22, -0.38. Children had a mean age of 7.8 years and treatment was for 6 months.
- One study showed there was no statistically significant difference in the number of children who achieved 0 to 1 wet nights a month between children treated with tablet desmopressin and those treated with tablet desmopressin and oxybutynin. Relative risk 0.96, 95% CI 0.61, 1.51. Children had a mean age of 7.8 years and treatment was for 6 months.
- One study showed there was no statistically significant difference in the number of wet nights per week at the end of treatment between children treated with tablet desmopressin and those treated with tablet desmopressin and oxybutynin. Mean difference -0.23, 95% CI -0.91, 0.45. Children had a mean age of 7.8 years and treatment was for 6 months.

Low dose tablet desmopressin compared high dose tablet desmopressin

Schulman (2001)¹³⁶, Skoog (1997)¹³⁹

- Two studies showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with 200 microgram tablet desmopressin and those treated with 400 microgram tablet desmopressin. Relative risk 0.32, 95% CI 0.09, 1.12. Children had a mean age of 9.1 to 11 years and treatment length was 2 to 6 weeks.
- Two studies showed there was no statistically significant difference in the number of wet in the last 2 weeks of treatment between children treated with 200 microgram tablet desmopressin and those treated with 400 microgram tablet desmopressin. Mean difference 0.5, 95% CI -0.24, 1.24. Children had a mean age of 9.1 to 11 years and treatment length was 2 to 6 weeks.
- Two studies showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with 200 microgram tablet desmopressin and those treated with 600 microgram tablet desmopressin. Relative risk 0.65, 95% CI 0.16, 2.62. Children had a mean age of 9.1 to 11 years and treatment length was 2 to 6 weeks.
- Two studies showed there was no statistically significant difference in the

number of wet in the last 2 weeks of treatment between children treated with 200 microgram tablet desmopressin and those treated with 600 microgram tablet desmopressin. Mean difference 0.04, 95% CI -0.94, 1.01. Children had a mean age of 9.1 to 11 years and treatment length was 2 to 6 weeks.

- Two studies showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with 400 microgram tablet desmopressin and those treated with 600 microgram tablet desmopressin. Relative risk 2.02, 95% CI 0.72, 5.66. Children had a mean age of 9.1 to 11 years and treatment length was 2 to 6 weeks.
- Two studies showed there was no statistically significant difference in the number of wet in the last 2 weeks of treatment between children treated with 400 microgram tablet desmopressin and those treated with 600 microgram tablet desmopressin. Mean difference -0.45, 95% CI -1.42, 0.53. Children had a mean age of 9.1 to 11 years and treatment length was 2 to 6 weeks.

Tablet desmopressin compared to melt desmopressin

Lottmann (2007)⁹³

One study showed there was no statistically significant difference in the number of wet nights per week at the end of treatment between children treated with tablet desmopressin and those treated with melt desmopressin. Mean difference -0.02, 95% CI -0.52, 0.48. Children had a mean age of 9.6 years and treatment length was 3 weeks.

All types of desmopressin compared to enuresis alarms

Ng (2005)¹¹⁵, **Wille (1986)**¹⁶⁷

- Two studies showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with desmopressin and those treated with enuresis alarms. Relative risk 1.17, 95% CI 0.46, 2.99. Children were aged over 6 years and treatment was for 3 months.
- Two studies showed there was no statistically significant difference in the mean number of wet nights per week at the end of treatment between children treated with desmopressin and those treated with enuresis alarms. Mean difference 0.46, 95% CI -0.62, 1.53. Children were aged over 6 years, Wille (1986) and had a mean age of 9.5 years, Ng (2005), and treatment was for 3 months.
- One study, Wille (1986), showed that children treated with desmopressin had a faster response compared to children treated with an enuresis alarm. Wille (1986) considered a response to be the number of dry nights.
- One study, Ng (2005), showed that children treated with an enuresis alarm had a faster response compared to children treated with desmopressin. Ng (2005) considered a response to be a reduction in the number of wet nights.
- Two studies showed after treatment children treated with an enuresis alarm had a continued higher response compared to children treated with desmopressin. Ng (2005) considered a response to be a reduction in the number of wet nights and Wille (1986) considered a response to be the number of dry nights. Children were aged over 6 years and treatment was for 3 months. Ng (2005) considered 200 microgram tablet desmopressin and Wille (1986) considered 200 micro grams intranasal desmopressin.

- Two studies showed there was no statistically significant difference in the number of children who dropped out of the trial between children treated with desmopressin and those treated with enuresis alarms. Relative risk 1.47, 95% CI 0.04, 51.07. Children were aged over 6 years and treatment was for 3 months.

Ng (2005)¹¹⁵

- One study showed there was no statistically significant difference in the mean number of wet nights per week at the end of follow up between children treated with desmopressin and those treated with enuresis alarms. Mean difference 0.9, 95% CI -0.38, 2.18. Children had a mean age of 9.5 years and treatment was for 3 months.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with desmopressin and those treated with enuresis alarms. Relative risk 10.06, 95% CI 0.66, 153.71. Children had a mean age of 9.5 years and treatment was for 3 months.

Studies include children with monosymptomatic nocturnal enuresis

The quality of evidence for outcomes was low or very low except for outcome 14 dry nights for the comparison between 600 micrograms desmopressin and placebo where quality was moderate.

Intranasal desmopressin

Longstaffe (2000)⁹²

- One study showed there was no statistically significant difference in the number of children who dropped out of the trial between the children treated with intranasal desmopressin and those treated with enuresis alarms. Relative risk 0.64, 95% CI 0.22, 1.83. Children were aged over 6 years and treatment length was 6 months.

Longstaffe (2000)⁹²

- One study showed that giving children treatment for nocturnal enuresis (20 micro grams intranasal desmopressin or enuresis alarm) improved their psychological scores in both treatment groups. Children were age over 7 years and the length of treatment was 6 months.

Longstaffe (2000)⁹²

- One study showed that giving children treatment for nocturnal enuresis (20 micro grams intranasal desmopressin or placebo) improved their psychological scores in both treatment groups. Children were age over 7 years and the length of treatment was 6 months.
- One study showed there was no statistically significant difference in the number of children who dropped out of the trial between the children treated with 20 micro grams intranasal desmopressin and those treated with placebo. Relative risk 1.27, 95% CI 0.36, 4.51. Children were aged over 7 years and treatment length was 6 months.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with intranasal desmopressin and those treated enuresis alarms. Relative risk 0.84, 95% CI 0.6, 1.18. Children were aged over 6 years and treatment length was 6 months.

Longstaffe (2000)⁹², **Rushton (1995)**¹³²

- Two studies showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with 20 micro grams and children treated with placebo. Relative risk 2.83, 95% CI 0.35, 22.68. Children in Longstaffe (2000) were aged over 7 years and treatment length was 6 months; children in Rushton (1995) had a mean age of 9.7 years and treatment length was 4 weeks

Rushton (1995) (Rushton et al. 749-53)

- One study showed that children treated with 20 micro grams intranasal desmopressin had fewer wet nights in the last 2 weeks of treatment compared to those who were treated with placebo. Mean difference -1.88, 95% CI -3.51, -0.25. Children had a mean age of 9.7 years and treatment length was 4 weeks.
- One study showed children treated with 40 micro grams intranasal desmopressin were more likely to achieve 14 consecutive dry nights than those treated with placebo. Relative risk 9.59, 95% CI 1.28, 72.04. Children had a mean age of 9.7 years and treatment length was 4 weeks.
- One study showed that children treated with 40 micro grams intranasal desmopressin had fewer wet nights in the last 2 weeks of treatment

compared to those who were treated with placebo. Mean difference -2.25, 95% CI -4, -0.5. Children had a mean age of 9.7 years and treatment length was 4 weeks.

Tablet desmopressin

Yap (1998)¹⁶⁹

- One showed children treated with 400 micrograms tablet desmopressin were more likely to achieve 14 consecutive dry nights than those treated with placebo. Relative risk 3.29, 95% CI 1.63, 6.62. Children had an age range of 7 to 18 and treatment length was 5 weeks.
- One showed that children treated with 400 micrograms tablet desmopressin had fewer wet nights per week at the end of treatment compared to those who were treated with placebo. Mean difference -2, 95% CI -3.15, -0.85. Children had an age range of 7 to 18 years and treatment length was 5 weeks.

Desmopressin (intranasal or tablet)

Tuygun (2007)¹⁵¹

- One study showed there was no statistically significant difference in the number of children who achieved a greater than 90% reduction in the number of wet nights between the children treated with desmopressin (intranasal or tablet) and those treated with an enuresis alarm. Relative risk 0.89, 95% CI 0.6, 1.33. Children had a median age of 8.6 to 8 years and treatment was for 3 months.
- One study showed there was no statistically significant difference in the number of children who achieved a 50 to 90% reduction in the number of wet nights between the children treated with desmopressin (intranasal or tablet) and those treated with an enuresis alarm. Relative risk 1.19, 95% CI 0.59, 2.41. Children had a median age of 8.6 to 8 years and treatment was for 3 months.
- One study showed children treated with an enuresis alarm had fewer wet nights in the month after treatment compared to those treated with desmopressin (intranasal or tablet). Mean difference 7.29, 95% CI 2.67, 11.91. Children had a median age of 8.6 to 8 years and treatment was for 3 months.

- One study showed children treated with an enuresis alarm were less likely to relapse at 6 months compared to those treated with desmopressin (intranasal or tablet). Relative risk 1.93, 95% CI 1.08, 3.45. Children had a median age of 8.6 to 8 years and treatment was for 3 months.

All types of desmopressin compared to enuresis alarms

Longstaffe (2000)⁹², Tuygun (2007)¹⁵¹

- Two studies showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with desmopressin and those treated with enuresis alarms. Relative risk 0.96, 95% CI 0.73, 1.25. Children were aged over 6 years and treatment was for 3 to 6 months.

Tuygun (2007)¹⁵¹

- One study showed there was no statistically significant difference in the number of children who achieved a 50 to 90% reduction in the number of wet nights between the children treated with desmopressin (intranasal or tablet) and those treated with an enuresis alarm. Relative risk 1.19, 95% CI 0.59, 2.41. Children had a median age of 8.6 to 8 years and treatment was for 3 months.
- One study showed children treated with an enuresis alarm had fewer wet nights in the month after treatment compared to those treated with desmopressin (intranasal or tablet). Mean difference 7.29, 95% CI 2.67, 11.91. Children had a median age of 8.6 to 8 years and treatment was for 3 months.
- One study showed children treated with an enuresis alarm were less likely to relapse at 6 months compared to those treated with desmopressin (intranasal or tablet). Relative risk 1.93, 95% CI 1.08, 3.45. Children had a median age of 8.6 to 8 years and treatment was for 3 months.

Longstaffe (2000)⁹²

- One study showed there was no statistically significant difference in the number of children who dropped out of the trial between children treated with desmopressin and those treated with enuresis alarms. Relative risk 0.64, 95% CI 0.22, 1.83. Children were aged over 6 years and treatment was for 3 to 6 months.

Studies included younger children with bedwetting and possible daytime

symptoms

Intranasal desmopressin

Birkasova (1978) ¹³

- One study showed there was no difference in the number of children who achieved 14 consecutive dry nights between the children treated with 10 micrograms intranasal desmopressin and those treated with placebo. Both groups had 0 children achieving 14 consecutive dry nights. Children had a mean age of 6.6 and treatment length was 2 weeks.
- One study showed that children treated with 10 micrograms intranasal desmopressin had fewer wet nights per fortnight at the end of treatment compared to those who were treated with placebo. Mean difference -6.8, 95% CI -9.43, -4.17. Children had a mean age of 6.6 years and treatment length was 2 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with 40 micrograms intranasal desmopressin and those treated with placebo. Relative risk 11, 95% CI 0.64, 187.67. Children had a mean age of 6.6 and treatment length was 2 weeks.
- One study showed that children treated with 40 micrograms intranasal desmopressin had fewer wet nights during the last 2 weeks of treatment compared to those who were treated with placebo. Mean difference -6.8, 95% CI -9.43, -4.17. Children had a mean age of 6.6 years and treatment length was 2 weeks.

Low dose intranasal desmopressin compared to high dose intranasal desmopressin

Birkasova (1978) ¹³

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with 10 micrograms intranasal desmopressin and those treated with 40 micrograms intranasal desmopressin. Relative risk 0.09, 95% CI 0.01, 1.55. Children had a mean age of 6.6 and treatment length was 2 weeks.

Side effects of desmopressin

Desmopressin compared to placebo for children with bedwetting

Schulman (2001) ¹³⁶

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- One study showed there was no statistically significant difference in the number of children who had vomiting causing withdrawal between children treated with desmopressin and children treated with placebo. Relative risk 1.77, 95% CI 0.09, 36.12. Children had an age range of 5 to 14 years and treatment length was for 8 weeks.

Skoog (1997)¹³⁹

- One study showed there was no statistically significant difference in the number of children who had rhinitis, pharyngitis, infection, headache or fever between children treated with desmopressin and children treated with placebo. Relative risk 1.11, 95% CI 0.66, 1.88. Children had a mean age of 9.1 to 9.5 years and had 6 weeks of treatment.

Desmopressin compared to melt desmopressin for children with monosymptomatic nocturnal enuresis

Lottmann (2007)⁹³

- One randomised controlled trial showed there was no statistically significant difference in the number of children with headaches between children treated with melt desmopressin and children treated with tablet desmopressin. Relative risk 13, 95% CI 0.74, 227.97. Children had a mean age of 9.6 years and had 6 weeks treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with diarrhoea between children treated with melt desmopressin and children treated with tablet desmopressin. Relative risk 7, 95% CI 0.37, 133.93. Children had a mean age of 9.6 years and had 6 weeks treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with viral gastroenteritis between children treated with melt desmopressin and children treated with tablet desmopressin. Relative risk 7, 95% CI 0.37, 133.93. Children had a mean age of 9.6 years and had 6 weeks treatment.

NCGC network meta-analysis (see appendix F)

For children with bedwetting and possible daytime symptoms

- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with combined desmopressin and amitriptyline and no treatment / placebo.**

Relative risk 9.481, 95% CI 6.444, 9.667. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.

- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with combined desmopressin and oxybutynin and no treatment / placebo. Relative risk 8.141, 95% CI 3.539, 9.53. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**
- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with desmopressin and no treatment / placebo. Relative risk 8.641, 95% CI 4.681, 9.569. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**

For children with bedwetting only

- **The NCGC NMA showed there was no statistically significant difference in the number of children who achieved a full response between children treated with nasal desmopressin and no treatment / placebo. Relative risk 2.785, 95% CI 0.387, 7.743. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**
- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with tablet desmopressin and no treatment / placebo. Relative risk 7.281, 95% CI 3.727, 9.109. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**
- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with combined tablet desmopressin and alarm and no treatment / placebo. Relative risk 8.519, 95% CI 3.567, 9.578. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**
- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with combined tablet desmopressin and oxybutynin and no treatment / placebo. Relative risk 7,640, 95% CI 2.012, 9.525. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**

For estimates of treatment effect relative to other active comparators, please see section 24.4 in chapter 24.

13.2.5 Health economic evidence statements

NCGC economic evaluation (see appendix G)

- An intervention sequence starting with desmopressin (and followed by alarm and then by desmopressin alone or combined with anticholinergic) may be cost-effective in the treatment of children with bedwetting starting at age 7 years. This evidence has potentially serious limitations and direct applicability.
- An intervention sequence starting with desmopressin (and followed by alarm and then by desmopressin alone or combined with anticholinergic) is very unlikely to be cost-effective in the treatment of children with bedwetting starting at age 5 years. This evidence has potentially serious limitations and direct applicability.
- Desmopressin is a cost-effective initial treatment for children starting treatment at ages 5 or 7 years for whom alarm-based interventions are not suitable. This evidence has potentially serious limitations and direct applicability.

13.2.6 Evidence to recommendations

Relative values of different outcomes

The GDG considered the children and parents or carers starting treatment for bedwetting were seeking an outcome of sustained dryness. A number of different outcomes were used to capture this: the outcome of 14 consecutive dry nights, reduction in wet nights and the mean number of wet nights allow evaluation of the effectiveness of treatment. Follow up rates, where available, can indicate sustained dryness.

Trade off between clinical benefit and harms

Side effect data was collected from RCTs or cohort studies. The consensus of the GDG was that desmopressin was safe as long as child and family understood and could comply with the need for fluid restriction.

Economic consideration

Desmopressin was evaluated as part of original economic modelling undertaken for this guideline and was shown to be a potentially cost-effective first line treatment

option. The analysis showed that there was considerable uncertainty about which intervention was the most cost-effective first line option, and this was likely caused by the uncertainty around estimates of treatment effectiveness observed in the pair-wise and network meta-analyses. The GDG considered that given the substantial uncertainty between interventions, it would be reasonable to recommend first line treatment with alarm as it was consistently shown to be among less costly and still effective options. Treatment sequences that started with desmopressin were generally more costly than those starting with alarm, and the incremental benefit was highly uncertain. Therefore, the GDG felt that desmopressin should be reserved as a first line intervention only for children for whom alarms are not suitable. Desmopressin is likely to be the most cost-effective intervention compared to other treatments where short-term improvement is the goal. However, based on original modelling undertaken for this guideline, it is uncertain as to whether using desmopressin as a first line, long term treatment is cost-effective.

Quality of evidence (this includes clinical and economic)

The studies were of varying quality however the clinical evidence was supportive of using desmopressin as an effective treatment for children with bedwetting. There were some well conducted trials with relatively small confidence intervals. In other studies limitations were identified including; short treatment intervals, small sample size, (therefore under-powered to detect a difference between intervention groups with wide confidence intervals), and incomplete evidence (some studies did not give standard deviations and therefore mean difference and confidence intervals could not be calculated). One study was terminated earlier than planned due to amitriptyline and placebo ceasing to be available. There was no long-term follow up data identified for the effectiveness of desmopressin. Six out of sixteen studies were industry funded and nine out of sixteen did not report funding sources.

Other considerations

The GDG used the direct clinical comparisons, the network meta-analysis and the health economic evidence to inform their recommendations.

On study indicated direct equivalence of tablet desmopressin and oral dispersible (melt) desmopressin. The GDG noted the study was designed to assess the impact of patient choice and not to evaluate differences in effectiveness of the two forms of desmopressin. One of the issues for the GDG members was that some of the evidence comes from studies of intranasal desmopressin which is no longer recommended in this condition. The GDG, using indirect evidence from the evidence review and from their own professional experience and knowledge, considered it appropriate to recommend desmopressin in general rather than specify route.

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When comparing tablet desmopressin to placebo the GDG noted that a lower dosage is effective in a significant number of children. In the absence of effect at a lower dosage there is good evidence that effectiveness is increased by increasing dosage. The evidence for escalating dose is discussed in chapter 13.

Overall comparison of desmopressin to alarm in a bedwetting only and in MNE group shows desmopressin has a faster response; however alarm is associated with sustained success and lower likelihood of relapse. There is no significant difference between the two for achieving 14 dry nights or mean reduction in number of wet nights at the end of treatment. The lower likelihood of relapse was considered by the GDG to support alarm as first line treatment and use of desmopressin if alarm is not appropriate. The faster response to desmopressin makes it the choice of treatment if dryness is required to be of rapid onset.

Comparing tablet desmopressin to tablet desmopressin combined with an alarm, the evidence showed no difference in achieving 14 consecutive dry nights at the end of treatment. However, combining the two treatments reduces the mean number of wet nights at the end of treatment compared to each treatment in isolation and combination treatment had a faster and more sustained response compared to desmopressin alone.

The evidence did not support combination of antidepressants with tricyclic antidepressant drugs.

Dose and timing of desmopressin

The GDG included a recommendation about starting desmopressin at lower dose as some children will achieve benefit on this. Desmopressin is taken before bedtime but from clinical experience and their knowledge of pharmacokinetics literature the GDG considered it useful to suggest children and parents take desmopressin 1-2 hours earlier if there has been no response or a partial response. The importance of fluid restriction may need to be re-iterated in these circumstances.

Sustaining treatment for up to 6 months

The GDG considered that one well conducted RCT which compared tablet desmopressin with tablet desmopressin combined with oxybutynin did not show any difference after 6 months treatment but the number of children responding to treatment in both groups continued to increase at 1 month, 3 months and 6 months after treatment.

Use of desmopressin in children between 5 and 7

The GDG were interested in evidence for use of desmopressin in younger children. One study in a group of children mean age 6.6 years showed that a short course of

desmopressin reduces the mean number of wet nights during treatment but does not make a difference with regards to achieving 14 consecutive dry nights. There was no follow-up data. The GDG considered that desmopressin could be used in children between 5 and 7 years, particularly if short term treatment was necessary.

Use of desmopressin in children with bedwetting and daytime symptoms

The evidence review indicated that children with bedwetting and daytime symptoms were likely to respond to desmopressin. The GDG considered from clinical experience that this group might not have as good a response to desmopressin as children with bedwetting alone.

Use of desmopressin in children with sickle cell disease, behavioural, attentional and emotional disorders.

Children with sickle cell disease were included as a subgroup as bedwetting is common and the GDG reported that there can be reluctance to use desmopressin in this group because of possible effects of desmopressin. Children with sickle cell disease can lose their concentrating ability of their kidneys resulting in high urine output. One study was identified which considered the side effects of desmopressin in children with sickle cell disease. The study did not identify any side effects different to those seen in children without sickle cell disease. The GDG discussed children with sickle cell disease could be treated with desmopressin if they could comply with the fluid restriction requirements for administration of desmopressin.

There was no specific evidence regarding the use of desmopressin in children with behavioural and attentional disorders and the GDG considered that the important consideration in assessment should be the child's ability to comply with fluid restrictions.

13.2.7 Recommendations

13.2.7.1 Offer desmopressin to children with bedwetting if:

- *rapid onset and/or short-term improvement in bedwetting is the priority of treatment **or***
- *an alarm is inappropriate or undesirable [1.10.1]*

- 13.2.7.2 *Do not exclude desmopressin as an option for the management of bedwetting in children who also have daytime symptoms. However, do not use desmopressin in the treatment of children who only have daytime wetting.[1.10.2]*
- 13.2.7.3 *In children who have failed to achieve complete dryness after 1 to 2 weeks on the initial dose of desmopressin (200 micrograms for Desmotabs and 120 micrograms for DesmoMelt), consider increasing the dose (to 400 micrograms of Desmotabs and 240 micrograms of Desmomelt).[1.10.3]*
- 13.2.7.4 *Assess the response to desmopressin at 4 weeks and continue treatment for 3 months if there are signs of a response. Consider stopping if there are no signs of response. Signs of response include*
- smaller wet patches
 - fewer wetting episodes per night
 - fewer wet nights.[1.10.4]
- 13.2.7.5 *Consider desmopressin for children between 5 and 7 years if treatment is required and an alarm is inappropriate or undesirable.[1.10.5]*
- 13.2.7.6 *Do not exclude desmopressin as an option for the treatment of bedwetting in children with sickle cell disease if an alarm is inappropriate or undesirable and they can comply with night-time fluid restriction. Provide advice about withdrawal of desmopressin at times of sickle cell crisis.[1.10.6]*
- 13.2.7.7 *Do not exclude desmopressin as an option for the treatment of bedwetting in children with emotional, attention or behavioural problems or developmental and learning difficulties if an alarm is inappropriate or undesirable and they can comply with night-time fluid restriction.[1.10.7]*
- 13.2.7.8 *Consider advising that desmopressin should be taken 1–2 hours before bedtime in children with bedwetting that has either partially responded or not responded to desmopressin taken at bedtime. Ensure that the child can comply with fluid restriction from 1 hour before the drug is taken.[1.10.10]*
- 13.2.7.9 *Consider continuing treatment with desmopressin for children with bedwetting that has partially responded, as bedwetting may improve for up to 6 months after starting treatment.[1.10.11]*

13.2.8 Supporting recommendations - Evidence to recommendations

Relative values of different outcomes

No evidence was identified

Trade off between clinical benefit and harms

No evidence was identified.

Economic considerations

No economic evidence was identified to inform these recommendations. The GDG considered that there was no evidence of need to monitor weight, serum electrolytes, blood pressure and urine osmolality in children with bedwetting being treated with desmopressin. A recommendation to discourage this activity is likely to represent a more cost-effective use of NHS resources.

Quality of evidence (this includes clinical and economic)

No evidence was identified.

Other considerations

The GDG discussed the lack of long term data for the effectiveness of desmopressin. From clinical and patient experience it was discussed that desmopressin may not lead to long term dryness without treatment and therefore this should be discussed with patients when being prescribed desmopressin in the treatment of bedwetting.

The GDG considered that there was no evidence of need to monitor weight, serum electrolytes, blood pressure and urine osmolality in children being treated with desmopressin. They considered that this idea may have arisen because of the other clinical conditions for which desmopressin may be used.

When used as initial treatment, desmopressin can be stopped or gradually withdrawn.

The GDG used their experience as health care professionals treating patients with bedwetting and as patient members to develop recommendations to cover the areas that they considered important when advising children and families.

13.2.9 Supporting recommendations

13.2.9.1 Do not routinely measure weight, serum electrolytes, blood pressure and urine osmolality in children being treated with desmopressin for bedwetting.[1.10.8]

13.2.9.2 If offering desmopressin for bedwetting in children, inform the child and parents or carers:

- *that many children, but not all, will experience a reduction in wetness*
- *how desmopressin works*
- *of the importance of fluid restriction from 1 hour before until 8 hours after taking desmopressin*
- *that it should be taken at bedtime*
- *if appropriate, how to increase the dose if there is an inadequate response to the starting dose*
- *that many children, but not all, will relapse when treatment is withdrawn*
- *to continue treatment with desmopressin for 3 months*

- *that repeated courses of desmopressin can be used.[1.10.9]*

14 Anticholinergic medication for the management of Nocturnal Enuresis

14.1 Introduction

What are they? These are a group of medicines that have an effect on the bladder. Oxybutynin is the medicine that is commonly used in children. Anticholinergic medicine reduces the number of involuntary bladder contractions and also has a relaxant effect on the smooth muscle of the bladder.

How do they work? Anticholinergics have the effect of decreasing the urge to pass urine in children with frequency or unstable bladders. It also allows the bladder to hold more urine. Oxybutynin is a short acting anticholinergic and needs to be given up to three times a day where treatment of day and night time urinary symptoms is required.

How is it given? For children with both daytime urinary symptoms and bedwetting oxybutynin can be given as an elixir or a tablet. Before sleep the dose can be increased to 5 - 6 mg or 10mls elixir and given at the same time as Desmopressin. Over 12 years the doses can be doubled.

Side effects and contraindications In general anticholinergics are very safe and in low doses (as starting doses above) are less likely to have side effects. The main side effects are dry mouth, headaches, constipation, retention of urine and very occasionally unusual behaviour or night terrors. All these side effects resolve when medication is stopped. Children also on treatment for constipation may need their laxative dose increased. Anticholinergics may be contraindicated in children who are known not to empty their bladders well as this problem can be made worse.

14.2 What is the clinical and cost effectiveness of anticholinergic medication for children and young people under 19 years who have nocturnal enuresis?

14.2.1 Evidence review

14.2.1.1 Oxybutynin compared to imipramine for children with bedwetting

One randomised control trial **Esmaeili (2008)**⁵¹ compared 3.75 to 5 mg oxybutynin to 10 to 25 mg imipramine.

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Table 14-1: Oxybutynin compared to imipramine - Clinical summary of findings

Outcome	Oxybutynin	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	6/26 (23.1%)	4/29 (13.8%)	RR 1.67 (0.53 to 5.28)	92 more per 1000 (from 65 fewer to 591 more)	VERY LOW
Mean number of wet nights per week during treatment	26	29	-	MD -1 (-1.98 to -0.02)	VERY LOW

14.2.1.2 Oxybutynin compared to oxybutynin and imipramine for children with bedwetting

One randomised control trial **Esmaeili (2008)**⁵¹ compared 3.75 to 5 mg oxybutynin to 3.75 to 5 mg oxybutynin and 10 to 25 mg imipramine.

Table 14 -2: Oxybutynin compared to oxybutynin and imipramine - Clinical summary of findings

Outcome	Oxybutynin	Oxybutynin and imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	6/26 (23.1%)	14/34 (41.2%)	RR 0.56 (0.25 to 1.26)	181 fewer per 1000 (from 309 fewer to 107 more)	VERY LOW
Mean number of wet nights per week during treatment	26	34	-	MD 1.1 (0.27 to 1.93)	VERY LOW

14.2.1.3 Oxybutynin compared to placebo for children with monosymptomatic nocturnal enuresis

One randomised control trial **Tahmaz (2000)**¹⁴⁵ compared 5 mg 3x/day oxybutynin to placebo.

Table 14-3: Oxybutynin compared to placebo for children with monosymptomatic NE - Clinical summary of findings

Outcome	Oxybutynin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved >90% improvement in the number of dry nights dry nights	6/16 (37.5%)	5/23 (21.7%)	RR 1.73 (0.63 to 4.69)	158 more per 1000 (from 80 fewer to 801 more)	VERY LOW
Number of children who achieved 50 to 90% improvement in the number of dry nights	6/16 (37.5%)	8/23 (34.8%)	RR 1.08 (0.46 to 2.51)	28 more per 1000 (from 188 fewer to 525 more)	VERY LOW
Number of children who relapsed at 6 months	5/6 (83.3%)	2/5 (40%)	RR 2.08 (0.67 to 6.46)	432 more per 1000 (from 132 fewer to 1000 more)	VERY LOW

14.2.1.4 *Oxybutynin compared to imipramine for children with monosymptomatic nocturnal enuresis*

One randomised control trial **Tahmaz (2000)**¹⁴⁵ compared oxybutynin to imipramine.

Table 14 -4: Oxybutynin compared to imipramine for children with monosymptomatic NE - Clinical summary of findings

Outcome	Oxybutynin	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved >90% improvement in the number of dry nights dry nights	6/16 (37.5%)	7/14 (50%)	RR 0.75 (0.33 to 1.71)	125 fewer per 1000 (from 335 fewer to 355 more)	VERY LOW
Number of children who achieved 50 to 90% improvement in the number of dry nights	6/16 (37.5%)	5/14 (35.7%)	RR 1.05 (0.41 to 2.7)	18 more per 1000 (from 211 fewer to 607 more)	VERY LOW

Number of children who relapsed at 6 months	5/6 (83.3%)	5/7 (71.4%)	RR 1.17 (0.65 to 2.1)	121 more per 1000 (from 250 fewer to 785 more)	VERY LOW
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14.2.1.5 *Oxybutynin compared to oxybutynin and imipramine for children with monosymptomatic nocturnal enuresis*

One randomised control trial **Tahmaz (2000)**¹⁴⁵ compared oxybutynin to oxybutynin and imipramine. Children had 5 mg oxybutynin 3 times a day or 5 mg oxybutynin 3 times a day and 0.9 to 1.5 mg/kg/day imipramine.

Table 14-5: Oxybutynin compared to oxybutynin and imipramine for children with monosymptomatic NE - Clinical summary of findings

Outcome	Oxybutynin	Oxybutynin and imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved >90% improvement in the number of dry nights	6/16 (37.5%)	16/24 (66.7%)	RR 0.56 (0.28 to 1.12)	293 fewer per 1000 (from 480 fewer to 80 more)	VERY LOW
Number of children who achieved 50 to 90% improvement in the number of dry nights	6/16 (37.5%)	6/24 (25%)	RR 1.5 (0.59 to 3.83)	125 more per 1000 (from 103 fewer to 708 more)	VERY LOW
Number of children who relapsed at 6 months	5/6 (83.3%)	4/16 (25%)	RR 3.33 (1.33 to 8.37)	582 more per 1000 (from 83 more to 1000 more)	VERY LOW

14.2.1.6 *Oxybutynin compared to placebo for children with monosymptomatic nocturnal enuresis*

One randomised controlled trial **Tahmaz (2000)**¹⁴⁵ compared oxybutynin to placebo. Children had 5 mg oxybutynin 3 times a day.

Table 14-6: Oxybutynin compared to placebo - Clinical summary of findings

Outcome	Oxybutynin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children with dry mouth or nausea	4/16 (25%)	4/23 (17.4%)	RR 1.44 (0.42 to 4.92)	77 more per 1000 (from 101 fewer to 682 more)	VERY LOW

14.2.1.7 Oxybutynin compared to imipramine for children with monosymptomatic nocturnal enuresis

One randomised controlled trial **Tahmaz (2000)**¹⁴⁵ compared oxybutynin to placebo. Children had 5 mg oxybutynin 3 times a day or 0.9 to 1.5 mg/kg/day imipramine.

Table 14-7: Oxybutynin compared to imipramine - Clinical summary of findings

Outcome	Oxybutynin	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children with dry mouth or nausea	4/16 (25%)	3/14 (21.4%)	RR 1.17 (0.31 to 4.34)	36 more per 1000 (from 148 fewer to 715 more)	VERY LOW

14.2.1.8 Oxybutynin compared to oxybutynin and imipramine for children with monosymptomatic nocturnal enuresis

One randomised controlled trial **Tahmaz (2000)**¹⁴⁵ compared oxybutynin to placebo. Children had 5 mg oxybutynin 3 times a day or 5 mg oxybutynin 3 times a day and 0.9 to 1.5 mg/kg/day imipramine.

Table 14-8: Oxybutynin compared to oxybutynin and imipramine - Clinical summary of findings

Outcome	Oxybutynin	Oxybutynin and imipramine	Relative risk (95% CI)	Absolute effect
Number of children with dry mouth or nausea	4/16 (25%)	7/24 (29.2%)	RR 0.86 (0.3 to 2.46)	41 fewer per 1000 (from 204 fewer to 426 more)

14.2.2 Network Meta-Analysis

Anticholinergic medication was amongst the interventions included in a network meta-analysis of interventions used for nocturnal enuresis. The summary of results of this analysis is presented in chapter 24 and a detailed description of the analysis is presented in appendix F. If studies did not meet the inclusion criteria of the network

meta-analysis protocol as stated in appendix F they were not included in the network meta-analysis

14.2.3 Health economic evidence review

Given the lack of published evidence assessing the cost-effectiveness of different interventions, including anticholinergics, used in the treatment of bedwetting, the GDG identified this area as high priority for original economic analysis. Therefore, a cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK National Health Service and Personal Social Services perspective. The time horizon for the analysis was 13 years, modelling patients from the time they entered at age 7 years until they reached age 20.

A summary of the analysis is provided below. The full report is presented in appendix G.

Summary of results

The results of the probabilistic sensitivity analysis are summarised in table 14-9 in terms of mean total costs and mean total QALYs and mean net benefit for each treatment sequence, where each mean is the average of 20,000 simulated estimates. The option with the greatest mean net benefit is the most cost-effective at a specified threshold (for example, £20,000). The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

Table 14-9: Basecase probabilistic sensitivity analysis results

Treatment sequence	Mean cost	Mean QALYs	Net Benefit (threshold=£20,000 per QALY)	Probability that strategy is most cost-effective (threshold =£20,000 per QALY)
No Treatment	£0	19.734	£394,684	0.0%
Alarm - Imipramine	£206	19.901	£397,816	0.4%
Imipramine - Desmopressin	£406	19.914	£397,875	0.0%
Imipramine - Desmopressin - Desmopressin+Anticholinergic	£514	19.922	£397,929	0.0%
Desmopressin - Imipramine	£298	19.912	£397,943	0.7%
Imipramine - Alarm - Desmopressin	£374	19.927	£398,169	0.0%
Imipramine - Alarm - Desmopressin - Desmopressin+Anticholinergic	£434	19.932	£398,203	0.0%
Desmopressin - Alarm - Imipramine	£304	19.952	£398,729	0.3%
Alarm - Desmopressin - Imipramine	£275	19.955	£398,814	0.1%

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Alarm - Imipramine - Desmopressin	£310	19.959	£398,877	0.0%
Alarm - Imipramine - Desmopressin - Desmopressin+Anticholinergic	£367	19.964	£398,910	0.0%
Desmopressin - Alarm+Desmopressin - Imipramine	£378	19.978	£399,178	3.1%
Desmopressin	£314	19.981	£399,297	7.1%
Alarm - Alarm+Desmopressin - Imipramine	£252	19.981	£399,357	13.1%
Desmopressin - Desmopressin+Anticholinergic	£426	19.990	£399,370	19.8%
Alarm - Desmopressin	£280	19.991	£399,549	4.9%
Desmopressin - Alarm+Desmopressin - Desmopressin	£410	19.998	£399,551	3.3%
Alarm - Desmopressin - Desmopressin+Anticholinergic	£346	19.997	£399,592	5.6%
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£433	20.002	£399,603	3.9%
Desmopressin - Alarm - Desmopressin	£350	19.998	£399,609	7.7%
Alarm - Alarm+Desmopressin - Desmo	£258	19.995	£399,640	15.9%
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£281	19.996	£399,647	8.3%
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£373	20.001	£399,647	5.8%

The results of the incremental analysis in the probabilistic analysis, excluding dominated and extendedly dominated strategies, are presented in table 14-10.

Table 14-10: Incremental analysis of basecase probabilistic results with dominated and extendedly dominated sequences removed

Treatment sequence	Mean cost (£)	Incremental Cost (£)	Mean QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		19.73421		
Alarm - Alarm+Desmopressin - Desmo	£258	£258	19.99489	0.26068	£988
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£282	£24	19.9964	0.00151	£15,828
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£373	£91	20.00099	0.00459	£19,891
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£433	£61	20.00183	0.00084	£72,143

Anticholinergics alone were not included among treatment sequences modelled. The results from the network meta-analysis did not show oxybutynin to be very effective on its own and the GDG did not think it was an appropriate treatment for

bedwetting in isolation. The network meta-analysis results showed that the combination of desmopressin and anticholinergic may be an effective intervention. Therefore it was included as a possible treatment following a non-response or partial response to desmopressin alone.

The results of the economic modeling show that the addition of anticholinergic to desmopressin in patients who have not responded or who have had a partial response to desmopressin is likely to be cost-effective. The sustained use of this combination, with one-week breaks every three months, is also likely to be cost-effective in patients who experience repeated recurrence of bedwetting when treatment is withdrawn.

A series of sensitivity analyses were undertaken to test some of the assumptions feeding into the model and none of these affected the cost-effectiveness of the sequence alarm followed by combined alarm and desmopressin and then desmopressin alone compared to no treatment.

The economic analysis conducted and presented here represents the first undertaken to assess the cost-effectiveness of interventions used in the treatment of children with bedwetting. And although the analysis is directly applicable to decision making in the UK NHS, it has some potentially serious limitations, some of which may significantly impact the overall conclusions that can be drawn. The main limitations of the analysis are related to the fact that assumptions had to be made in the absence of evidence. Some of these key assumptions centre around:

- treatment effectiveness being independent of age
- health care resource use having been estimated by GDG
- utility weights having been estimated by GDG

A full discussion of these can be found in appendix G.

14.2.4 Evidence statements

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Studies include children with bedwetting only

Oxybutynin

Esmaeili (2008) ⁵¹

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with oxybutynin and those treated with imipramine. Relative risk 1.67, 95% CI 0.53, 5.28. Children had a mean age of 8.9 (sd 1.6) years and a treatment length of 1 month.

- One study showed children treated with oxybutynin had fewer wet nights per week during treatment than those treated with imipramine. Mean difference -1, 95% CI -1.98, -0.02. Children had a mean age of 8.9 (sd 1.6) years and a treatment length of 1 month.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between the children treated with oxybutynin and those treated with oxybutynin and imipramine. Relative risk 0.56, 95% CI 0.25, 1.26. Children had a mean age of 8.9 (sd 1.6) years and a treatment length of 1 month.
- One study showed children treated with oxybutynin and imipramine had fewer wet nights per week during treatment than those treated with oxybutynin. Mean difference 1.1, 95% CI 0.27, 1.93. Children had a mean age of 8.9 (sd 1.6) years and a treatment length of 1 month.

Studies include children with monosymptomatic nocturnal enuresis

Oxybutynin

Tahmaz (2000) ¹⁴⁵

- One study showed there was no statistically significant difference in the number of children who achieved >90% improvement in the number of dry nights between the children treated with oxybutynin and those treated with placebo. Relative risk 1.73, 95% CI 0.63, 4.69. Children had a mean age of 9.44 (sd 2.17) and treatment length was 3 months.
- One study showed there was no statistically significant difference in the number of children who achieved 50 to 90% improvement in the number of dry nights between children treated with oxybutynin and children treated with placebo. Relative risk 1.08, 95% CI 0.46, 2.51. Children had a mean age of 9.44 (sd 2.17) and treatment length was 3 months.
- One study showed there was no statistically significant difference in the number of children who relapsed at 6 months between the children treated with oxybutynin and those treated with placebo. Relative risk 2.08, 95% CI 0.67, 6.46. Children had a mean age of 9.44 (sd 2.17) and treatment length was 3 months.
- One study showed there was no statistically significant difference in the number of children who achieved >90% improvement in the number of dry nights between the children treated with oxybutynin and those treated with imipramine. Relative risk 0.75, 95% CI 0.33, 1.71. Children had a mean age of

9.44 (sd 2.17) and treatment length was 3 months.

- One study showed there was no statistically significant difference in the number of children who achieved 50 to 90% improvement in the number of dry nights between children treated with oxybutynin and children treated with imipramine. Relative risk 1.05, 95% CI 0.41, 2.7. Children had a mean age of 9.44 (sd 2.17) and treatment length was 3 months.
- One study showed there was no statistically significant difference in the number of children who relapsed at 6 months between the children treated with oxybutynin and those treated with imipramine. Relative risk 1.17, 95% CI 0.65, 2.1. Children had a mean age of 9.44 (sd 2.17) and treatment length was 3 months.
- One study showed there was no statistically significant difference in the number of children who achieved >90% improvement in the number of dry nights between the children treated with oxybutynin and those treated with oxybutynin and imipramine. Relative risk 0.56, 95% CI 0.28, 1.12. Children had a mean age of 9.44 (sd 2.17) and treatment length was 3 months.
- One study showed there was no statistically significant difference in the number of children who achieved 50 to 90% improvement in the number of dry nights between children treated with oxybutynin and children treated with oxybutynin and imipramine. Relative risk 1.5, 95% CI 0.59, 3.83. Children had a mean age of 9.44 (sd 2.17) and treatment length was 3 months.
- One study showed children treated with oxybutynin were more likely to relapse at 6 months compared to children treated with oxybutynin and imipramine. Relative risk 3.33, 95% CI 1.33, 8.37. Children had a mean age of 9.44 (sd 2.17) and treatment length was 3 months.

Side effects of oxybutynin

Tahmaz (2000) ¹⁴⁵

- One study showed there was no statistically significant difference in the number of children who had dry mouth or nausea between children treated with oxybutynin and children treated with placebo. Relative risk 1.44, 95% CI 0.42, 4.92. Children had a mean age of 9.44 (sd 2.17) years and had 3 months of treatment.

- One study showed there was no statistically significant difference in the number of children who had dry mouth or nausea between children treated with oxybutynin and children treated with imipramine. Relative risk 1.17, 95% CI 0.31, 4.34. Children had a mean age of 9.44 (sd 2.17) years and had 3 months of treatment.
- One study showed there was no statistically significant difference in the number of children who had dry mouth or nausea between children treated with oxybutynin and children treated with oxybutynin and imipramine. Relative risk 0.86, 95% CI 0.3, 2.46. Children had a mean age of 9.44 (sd 2.17) years and had 3 months of treatment.

NCGC network meta-analysis (see appendix F)

- **The NCGC NMA showed there was no statistically significant difference in the number of children who achieved a full response between children treated with oxybutynin and no treatment / placebo. Relative risk 1.696, 95% CI 0.153, 7.277. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**
- **The NCGC NMA showed there was no statistically significant difference in the number of children who experienced a recurrence of bedwetting at 6 months between children treated with oxybutynin and no treatment / placebo. Relative risk 0.5232, 95% CI 0.029, 8.444. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**

For estimates of treatment effect relative to other active comparators, please see section 24.4 in chapter 24.

14.2.5 Health economic evidence statements

NCGC economic evaluation (see appendix G)

The addition of an anticholinergic to desmopressin when desmopressin alone has only produced a partial response is likely to be cost-effective in the treatment of children with bedwetting. This evidence has potentially serious limitations and direct applicability.

14.2.6 Evidence to recommendations

Relative values of different outcomes

The GDG considered the children and parents or carers starting treatment for bedwetting were seeking an outcome of sustained dryness. A number of different

outcomes were used to capture this: the outcome of 14 consecutive dry nights, reduction in wet nights and the mean number of wet nights allow evaluation of the effectiveness of treatment. Follow up rates where available can indicate sustained dryness.

Trade off between clinical benefit and harms

The GDG considered that awareness of the possible side-effects of anticholinergics is important and constipation should be excluded or treated prior to commencement with an anticholinergic. This has particular importance as children with bedwetting may also have constipation. Behavioural issues may arise with anticholinergics.

Economic considerations:

The cost-effectiveness of treatment with anticholinergics alone was not explicitly considered as part of the economic modeling undertaken for this guideline. This was because the evidence did not show anticholinergics alone to be effective in the treatment of bedwetting, therefore other more effective interventions and combinations of interventions were the focus of the economic analysis.

One such combination was desmopressin and anticholinergic which the GDG thought might be a useful intervention for patients who have experienced only a partial response to desmopressin alone. This strategy was included in the economic modeling and was shown to be a potentially cost-effective combination in this particular population of partial responders to desmopressin.

Quality of evidence (this includes clinical and economic)

The quality of evidence overall was low and the population studied considered not to be the most likely population to respond to use of anticholinergic. Two studies were identified which evaluated the effectiveness of oxybutynin but the evidence for use of tolterodine was in treatment resistant population only. The population evaluated by the trials was children classified as bedwetting only children or monosymptomatic enuresis whereas, theoretically, the group of children who are more likely to benefit from anticholinergics are children with night-time wetting and daytime symptoms probably accounted for by an overactive bladder.

Other considerations

These recommendations regarding the use of anticholinergic medication were made using the direct evidence in this chapter, the direct evidence in chapter in treatment resistance (chapter 17), the network meta-analysis, the health economic analysis and the professional opinion of the GDG

Combination with desmopressin

One study which is reported in the desmopressin evidence review (Lee 2005) showed there was no difference in the success rates of tablet desmopressin and tablet desmopressin combined with oxybutynin after six months of treatment, suggesting the combination of desmopressin and oxybutynin in a population with bedwetting and daytime symptoms is as effective as desmopressin alone. Children on both regimes did have a reduction in bedwetting. The GDG considered that the combination of desmopressin and anticholinergic should only be initiated by a health care professional with expertise in this area. The use of this combination in children who have failed to respond to treatment is discussed in chapter 17.

14.2.7 Recommendations

The use of anticholinergics for bedwetting in children is discussed in the recommendations in this section. Not all anticholinergics have a UK marketing authorisation for treating bedwetting in children. If a drug without a marketing authorisation for this indication is prescribed, informed consent should be obtained and documented.

- 14.2.7.1 *Do not use an anticholinergic alone in children for the management of bedwetting in children without daytime symptoms.[1.12.1]*
- 14.2.7.2 *Consider an anticholinergic combined with desmopressin for bedwetting in children who also have daytime symptoms and have been assessed by a healthcare professional with expertise in prescribing the combination of an anticholinergic and desmopressin.[1.12.2].*
- 14.2.7.3 *Consider continuing treatment for children with bedwetting that has partially responded to desmopressin combined with an anticholinergic as bedwetting may continue to improve for up to 6 months after starting treatment.[1.12.4.]*
- 14.2.7.4 *If offering an anticholinergic combined with desmopressin for bedwetting in children, inform the child and parents or carers:*
- *that success rates are difficult to predict but that more children are drier with this combination than with desmopressin alone*
 - *that desmopressin and an anticholinergic can be taken together at the same time before bed*
 - *to continue treatment for 3 months*

- *that repeated courses can be used.[1.12.6]*

14.2.7.5 *Do not offer an anticholinergic combined with imipramine for the treatment of bedwetting in children.[1.12.7]*

15 Tricyclic medication and the management of bedwetting

15.1 Introduction

What are they? The tricyclic drugs have been used for treating bedwetting for many years. The need for close follow up and the potential for serious cardiac consequences in overdose mean they are considered for use in specialist centres only.

How do they work? Tricyclics have significant anticholinergic effects and thus have similar properties to Oxybutynin (see anticholinergics). They also have additional central effects which are not well understood but can be beneficial in preventing bedwetting in a group of children who have not responded to first line treatments.

How is it given? Imipramine is only available as tablets. To minimise side effects it is best started as a low dose and increased fortnightly to the maximum dose allowed for the age of the child. The single daily dose should be given around 3 hours before sleep. A course of treatment should last for 3 months maximum before reducing the dose slowly and stopping it for a week or so to assess progress.

Side effects and contraindications. Most children tolerate this medication without experiencing side effects. The main side effects are dry mouth, gastrointestinal symptoms and occasional behavioural changes. These resolve when the medication is stopped. The tricyclics have the potential to interact with other long term medications eg for epilepsy and this should be checked before starting treatment. Overdosage can cause serious cardiac arrhythmias (abnormalities of heart rhythm) and death. Tricyclics are contraindicated in children with a family history of early cardiac death or who have any evidence of cardiac disease.

15.2 What is the clinical and cost effectiveness of tricyclic medication for children and young people under 19 years who have bedwetting?

15.2.1 Evidence review

The studies included in the review had varying dosages of imipramine given, based on age or weight of the patient, with younger children being given 25 mg imipramine and older children being given 50 mg imipramine.

15.2.1.1 Imipramine compared to placebo

Fourteen randomised controlled trials compared imipramine to placebo; **Agarwala (1968)**¹, **Attenburrow (1984)**², **Batlam (1995)**¹⁰, **Drew (1966)**⁴⁴, **Fournier (1987)**

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⁶⁰, Harrison (1970) ⁷⁰, Hodes (1973) ⁷¹, Khorana (1972) ⁸², Kolvin (1972) ⁸³, Manhas (1967) ⁹⁶, Martin (1971) ⁹⁸, Poussaint (1965) ¹²⁰, Smellie (1996) ¹⁴⁰, and (1964) ¹⁴⁹.

Table 15 -1: Imipramine compared to placebo - Clinical summary of findings

Outcome	Imipramine	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	64/171 (37.4%)	12/168 (7.1%)	RR 4.81 (1.67 to 13.89)	271 more per 1000 (from 48 more to 915 more)	LOW
Number of children who had >80% improvement at the end of treatment	16/35 (45.7%)	5/27 (18.5%)	RR 2.47 (1.03 to 5.89)	272 more per 1000 (from 6 more to 905 more)	VERY LOW
Number of children who showed >50% improvement in the number of dry nights	27/45 (60%)	10/39 (25.6%)	RR 1.27 (0.06 to 27.63)	69 more per 1000 (from 241 fewer to 1000 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	9	12	-	MD -2.5 (-5.74 to 0.74)	LOW
Mean number of wet nights per week at the end of treatment (no sd)	129	100	-	not pooled	VERY LOW
Mean number of wet nights per 2 weeks during treatment	29	29	-	MD -2.3 (-4.19 to -0.41)	LOW
Mean number of wet nights during 26 nights of treatment	57	57	-	MD -6.3 (-8.6 to -4)	LOW
Mean number of wet nights per week at follow up	9	12	-	MD -1.5 (-4.85 to 1.85)	LOW
Mean number of wet nights per week at follow up (no sd)	35	27	-	not pooled	VERY LOW

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Number of children who dropped out	2/32 (6.3%)	0/32 (0%)	RR 5 (0.25 to 100.21)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
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15.2.1.2 Low dose imipramine compared to placebo

One randomised controlled trial **Martin (1971)**⁹⁸ compared 10 mg imipramine to placebo. The usual stated dosage (in the BNF) for imipramine in the treatment of nocturnal enuresis 25 mg imipramine for younger children and 50 mg imipramine for older children. It was therefore considered that a dosage of 10 mg imipramine compared to placebo should be evaluated separately from the usual higher dosage of imipramine compared to placebo.

Table 15-2: Low dose imipramine compared to placebo - Clinical summary of findings

Outcome	Low dose Imipramine	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights during 26 nights of treatment	57	57	-	MD -3.1 (-5.1 to -1.1)	VERY LOW

15.2.1.3 Low dose imipramine compared to high dose imipramine

One randomised controlled trial, **Martin (1971)**⁹⁸, compared 10 mg imipramine to 25 mg imipramine. The usual stated dosage for imipramine (in the BNF) in the treatment of nocturnal enuresis 25 mg imipramine for younger children and 50 mg imipramine for older children. It was therefore considered that the comparison of 10 mg imipramine to 25 mg imipramine should be evaluated separately.

Table 15-3: Low dose imipramine compared to high dose imipramine - Clinical summary of findings

Outcome	Low dose Imipramine	High dose Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights during 26 nights of treatment	57	57	-	MD 3.2 (1.3 to 5.1)	VERY LOW

15.2.1.4 Imipramine compared to desmopressin

Two randomised controlled trials **Vertucci (1997)**¹⁵⁸ and **Lee (2005)**⁹⁰ compared imipramine to desmopressin.

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Table 15-4: Imipramine compared to desmopressin - Clinical summary of findings

Outcome	Imipramine	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who dropped out	7/48 (14.6%)	3/49 (6.1%)	RR 2.38 (0.65 to 8.68)	84 more per 1000 (from 21 fewer to 468 more)	VERY LOW

Table 15- 5: Imipramine compared to desmopressin - Clinical summary of findings

Outcome	Imipramine	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	19/28 (67.9%)	25/29 (86.2%)	RR 0.79 (0.59 to 1.06)	181 fewer per 1000 (from 353 fewer to 52 more)	VERY LOW
Number of children who had 0-1 wet nights per month	3/25 (12%)	9/26 (34.6%)	RR 0.35 (0.11 to 1.13)	225 fewer per 1000 (from 308 fewer to 45 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	25	26	-	MD 1.4 (0.55 to 2.25)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	28	29	-	not pooled	VERY LOW
Mean number of wet nights per week after treatment with imipramine and desmopressin (separate treatments) (no sd)	28	29	-	not pooled	VERY LOW

15.2.1.5 *Imipramine compared to enuresis alarm*

Two randomised controlled trials, **Fournier (1987)**⁶⁰ and **Kolvin (1972)**⁸³ compared imipramine to enuresis alarm treatment.

Table 15-6: Imipramine compared to alarm - Clinical summary of findings

Outcome	Imipramine	Alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who had >80% improvement in the number of dry nights at the end of treatment	16/35 (45.7%)	17/32 (53.1%)	RR 0.86 (0.53 to 1.4)	74 fewer per 1000 (from 250 fewer to 212 more)	VERY LOW
Number of children who dropped out	1/8 (12.5%)	1/8 (12.5%)	RR 1 (0.07 to 13.37)	0 fewer per 1000 (from 116 fewer to 1000 more)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	43	40	-	not pooled	VERY LOW
Mean number of wet nights per week at the end of follow up (no sd)	35	32	-	not pooled	VERY LOW

15.2.1.6 *Imipramine compared to imipramine combined with enuresis alarm*

One randomised controlled trial **Fournier (1987)**⁶⁰ compared imipramine to imipramine with an enuresis alarm.

Table 15-7: Imipramine compared to imipramine and alarm - Clinical summary of findings

Outcome	Imipramine	Imipramine and alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of drop outs at end of trial	0/8 (0%)	0/8 (0%)	not pooled	not pooled	LOW

Mean number of wet nights per week at follow-up (no SDs)	8	8	-	not pooled	VERY LOW
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15.2.1.7 Imipramine compared to desmopressin combined with oxybutynin

One randomised controlled trial **Lee (2005)**⁹⁰, compared imipramine to desmopressin combined with oxybutynin.

Table 15-8: Imipramine compared to desmopressin and oxybutynin - Clinical summary of findings

Outcome	Imipramine	Desmopressin and oxybutynin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who dropped out	7/48 (14.6%)	3/48 (6.3%)	RR 2.33 (0.64 to 8.49)	84 more per 1000 (from 23 fewer to 472 more)	VERY LOW

Table 15-9: Imipramine compared to desmopressin and oxybutynin - Clinical summary of findings

Outcome	Imipramine	Desmopressin and oxybutynin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who had 0-1 wet nights per month	3/25 (12%)	9/26 (34.6%)	RR 0.35 (0.11 to 1.13)	225 fewer per 1000 (from 308 fewer to 45 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	25	26	-	MD 1.43 (0.45 to 2.41)	VERY LOW

15.2.1.8 Amitriptyline compared to placebo

One randomised controlled trial, **Poussaint (1966)**¹²¹ compared amitriptyline to placebo.

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Table 15-10: Amitriptyline compared to placebo - Clinical summary of findings

Outcome	Amitriptyline	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment (no sd)	25	25	-	not pooled	LOW

15.2.1.9 Amitriptyline compared to desmopressin

One randomised controlled trial **Burke (1995)**¹⁹ compared amitriptyline to desmopressin.

Table 15-11: Amitriptyline compared to desmopressin - Clinical summary of findings

Outcome	Amitriptyline	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	3/14 (21.4%)	1/17 (5.9%)	RR 3.64 (0.42 to 31.27)	156 more per 1000 (from 34 fewer to 1000 more)	MODERATE
Number of children who dropped out of the trial	0/14 (0%)	3/17 (17.6%)	RR 0.17 (0.01 to 3.06)	146 fewer per 1000 (from 174 fewer to 363 more)	MODERATE
Mean number of wet nights per week at the end of treatment	14	17	-	MD -1.4 (-2.95 to 0.15)	MODERATE
Mean number of wet nights per week at the end of follow up	14	17	-	MD 0.1 (-1.67 to 1.87)	MODERATE

15.2.1.10 Amitriptyline compared to enuresis alarm

One randomised controlled trial, **Danquah (1975)**³⁸ compared amitriptyline to an enuresis alarm.

Table 15-12: Amitriptyline compared to alarm - Clinical summary of findings

Outcome	Amitriptyline	Alarm	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment (no sd)	10	10	-	not pooled	VERY LOW
Median number of days to arrest	10	10	-	not pooled	VERY LOW

15.2.1.11 Amitriptyline compared to amitriptyline combined with desmopressin

One randomised controlled trial, **Burke (1995)**¹⁹ compared amitriptyline to amitriptyline combined with desmopressin.

Table 15-13: Amitriptyline compared to amitriptyline and desmopressin - Clinical summary of findings

Outcome	Amitriptyline	Amitriptyline and desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	3/14 (21.4%)	5/14 (35.7%)	RR 0.6 (0.18 to 2.04)	143 fewer per 1000 (from 293 fewer to 371 more)	MODERATE
Number of children who dropped out of the trial	0/14 (0%)	3/14 (21.4%)	RR 0.14 (0.01 to 2.53)	184 fewer per 1000 (from 212 fewer to 327 more)	MODERATE
Mean number of wet nights per week at the end of treatment	14	14	-	MD 0 (-1.64 to 1.64)	MODERATE
Mean number of wet nights per week at the end of follow up	14	14	-	MD -1.2 (-3.46 to 1.06)	MODERATE

15.2.1.12 *Nortriptyline compared to placebo*

One randomised controlled trial **Lake (1968)**⁸⁷, compared nortriptyline to placebo.

Table 15-14: Nortriptyline compared to placebo - Clinical summary of findings

Outcome	Nortriptyline	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment (no sds)	54	54	-	not pooled	VERY LOW

15.2.1.13 *Imipramine compared to placebo for children with bedwetting*

One randomised controlled trial compared imipramine to placebo for children with bedwetting, **Tahmaz (2000)**¹⁴⁵

Table 15-15: Imipramine compared to placebo for children with bedwetting - Clinical summary of findings

Outcome	Imipramine	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	4/12 (33.3%)	1/12 (8.3%)	RR 4 (0.52 to 30.76)	249 more per 1000 (from 40 fewer to 1000 more)	VERY LOW
Number of children who had >90% improvement in the number of dry nights	7/14 (50%)	5/23 (21.7%)	RR 2.3 (0.9 to 5.86)	282 more per 1000 (from 22 fewer to 1000 more)	VERY LOW
Number of children who had 50 to 90% improvement in the number of dry nights	5/14 (35.7%)	8/23 (34.8%)	RR 1.03 (0.42 to 2.52)	10 more per 1000 (from 202 fewer to 529 more)	VERY LOW
Number of children who relapsed at 6 months	9/11 (81.8%)	3/6 (50%)	RR 1.79 (0.55 to 5.76)	395 more per 1000 (from 225 fewer to 1000 more)	VERY LOW

15.2.1.14 *Imipramine compared to desmopressin for children with bedwetting*

One randomised controlled trial **Lee (2005)**⁹⁰ compared imipramine to desmopressin for children with bedwetting.

Table 15-16: Imipramine compared to desmopressin - Clinical summary of findings

Outcome	Imipramine	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who had 0-1 wet nights per month	3/23 (13%)	14/23 (60.9%)	RR 0.21 (0.07 to 0.65)	481 fewer per 1000 (from 213 fewer to 566 fewer)	LOW
Mean number of wet nights per week at the end of treatment	23	23	-	MD 1.3 (0.38 to 2.22)	VERY LOW

15.2.1.15 *Imipramine compared to oxybutinin for children with bedwetting*

Two randomised controlled trials, **Esmaili (2008)**⁵¹ and **Tahmaz (2000)**¹⁴⁵ compared imipramine to oxybutynin for children with bedwetting. See GRADE table in chapter 14.

15.2.1.16 *Imipramine compared to enuresis alarm for children with bedwetting*

One randomised controlled trails, **Wagner (1982)**¹⁶⁰ compared imipramine to enuresis alarm treatment for children with bedwetting.

Table 15 -17: Imipramine compared to alarm - Clinical summary of findings

Outcome	Imipramine	Alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	4/12 (33.3%)	10/12 (83.3%)	RR 0.4 (0.17 to 0.93)	500 fewer per 1000 (from 58 fewer to 691 fewer)	VERY LOW

Number of children who relapsed at 6 months	4/4 (100%)	5/10 (50%)	RR 1.8 (0.93 to 3.48)	400 more per 1000 (from 35 fewer to 1000 more)	VERY LOW
Mean number of wet nights per week at end of treatment (no SDs)	12	12	-	not pooled	VERY LOW

15.2.1.17 Imipramine compared to imipramine combined with oxybutinin for children with bedwetting

Two randomised controlled trials, **Esmielli (2008)**⁵¹ and **Tahmaz (2000)**¹⁴⁵ compared imipramine to imipramine combined with oxybutynin for children with bedwetting.

See GRADE table in chapter 14.

15.2.1.18 Imipramine compared to desmopressin combined with oxybutinin for children with bedwetting

One randomised controlled trial **Lee (2005)**⁹⁰, compared imipramine to desmopressin combined with oxybutynin for children with bedwetting.

Table 15-18: Imipramine compared to desmopressin and oxybutynin - Clinical summary of findings

Outcome	Imipramine	Desmopressin and oxybutynin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who had 0-1 wet nights per month	3/23 (13%)	14/22 (63.6%)	RR 0.2 (0.07 to 0.62)	509 fewer per 1000 (from 242 fewer to 591 fewer)	LOW
Mean number of wet nights per week at the end of treatment	23	22	-	MD 1.07 (0.06 to 2.08)	VERY LOW

15.2.1.19 *Imipramine for children with monosymptomatic nocturnal enuresis*

One observational study, **Monda (1995)**¹⁰⁴ considered imipramine for children with monosymptomatic nocturnal enuresis. Children had 1 mg/kg imipramine, increased to 1.5 mg/kg if still wetting after 2 weeks, and was given 30 to 45 minutes before going to bed.

15.2.1.20 *Imipramine compared to placebo for children with severe wetting*

One randomised controlled trial compared imipramine to placebo for children with severe wetting, **Hagglund (1964)**⁶⁷.

Table 15-19: Imipramine compared to placebo for children with severe wetting - Clinical summary of findings

Outcome	Imipramine	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved >90% improvement in the number of dry nights	3/7 (42.9%)	0/8 (0%)	RR 7.88 (0.48 to 130.28)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

15.2.1.21 *Imipramine and placebo compared to placebo for children with severe wetting*

One randomised controlled trial compared imipramine and placebo to placebo for children with severe only wetting, **Forsythe (1969)**⁵⁹.

Table 15-20: Imipramine and placebo compared to placebo - Clinical summary of findings

Outcome	Imipramine and placebo	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	1/76 (1.3%)	1/85 (1.2%)	RR 1.12 (0.07 to 17.57)	1 more per 1000 (from 11 fewer to 199 more)	VERY LOW

Number of children who achieved greater than 50% improvement in the number of dry nights	22/76 (28.9%)	21/85 (24.7%)	RR 1.17 (0.7 to 1.95)	42 more per 1000 (from 74 fewer to 235 more)	VERY LOW
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15.2.1.22 Imipramine and placebo compared to nortriptyline placebo for children with severe wetting

One randomised controlled trial compared imipramine and placebo to nortriptyline and placebo for children with severe only wetting, **Forsythe (1969)**⁵⁹.

Table 15-21: Imipramine and placebo compared to nortriptyline and placebo - Clinical summary of findings

Outcome	Imipramine and placebo	Nortriptyline and placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	1/76 (1.3%)	1/86 (1.2%)	RR 1.13 (0.07 to 17.78)	2 more per 1000 (from 11 fewer to 201 more)	VERY LOW
Number of children who achieved greater than 50% improvement in the number of dry nights	22/76 (28.9%)	34/86 (39.5%)	RR 0.73 (0.47 to 1.14)	107 fewer per 1000 (from 209 fewer to 55 more)	VERY LOW

15.2.1.23 Nortriptyline and placebo compared to placebo for children with severe wetting

One randomised controlled trial compared nortriptyline and placebo to placebo for children with severe only wetting, **Forsythe (1969)**⁵⁹.

Table 15-22: Nortriptyline and placebo compared to placebo - Clinical summary of findings

Outcome	Nortriptyline and placebo	Placebo	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	1/86 (1.2%)	1/85 (1.2%)	RR 0.99 (0.06 to 15.55)	0 fewer per 1000 (from 11 fewer to 175 more)	VERY LOW
Number of children who achieved greater than 50% improvement in the number of dry nights	34/86 (39.5%)	21/85 (24.7%)	RR 1.6 (1.02 to 2.52)	148 more per 1000 (from 5 more to 375 more)	VERY LOW

15.2.2 Side effects of tricyclics for the treatment of bedwetting

15.2.2.1 Imipramine compared to placebo

Five randomised controlled trials, **Agarwala (1968)**¹, **Attenburrow (1984)**², **Batislam (1995)**¹⁰, **Manhas (1967)**⁹⁶ and **Martin (1971)**⁹⁸ compared imipramine to placebo. All studies considered 25 mg imipramine.

One randomised controlled trial, **Martin (1971)**⁹⁸ considered low dose (10 mg) imipramine compared to placebo.

Table 15- 23: Imipramine compared to placebo - Clinical summary of findings

Outcome	Imipramine	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children with anxiety	4/57 (7%)	1/57 (1.8%)	RR 4 (0.46 to 34.7)	54 more per 1000 (from 10 fewer to 607 more)	VERY LOW
Number of children with lethargy	4/9 (44.4%)	0/12 (0%)	RR 11.7 (0.71 to 192.98)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children with sleep disturbances	3/57 (5.3%)	3/57 (5.3%)	RR 1 (0.21 to 4.75)	0 fewer per 1000 (from 42 fewer to 199 more)	VERY LOW
Number of children with dizziness	1/29 (3.4%)	0/29 (0%)	RR 3 (0.13 to 70.74)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Number of children with giddiness	2/29 (6.9%)	1/27 (3.7%)	RR 1.86 (0.18 to 19.38)	32 more per 1000 (from 30 fewer to 680 more)	VERY LOW

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Number of children with dizziness and dry mouth	1/9 (11.1%)	0/12 (0%)	RR 3.9 (0.18 to 85.93)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Number of children with gastrointestinal	8/16 (50%)	0/12 (0%)	RR 13 (0.82 to 205.24)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children with upset stomach	2/9 (22.2%)	0/12 (0%)	RR 6.5 (0.35 to 120.8)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children with abdominal pain	4/86 (4.7%)	1/84 (1.2%)	RR 2.89 (0.46 to 18.13)	23 more per 1000 (from 6 fewer to 206 more)	MODERATE
Number of children with abdominal pain and epistaxis	1/29 (3.4%)	0/27 (0%)	RR 2.8 (0.12 to 65.93)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children with vomiting and drowsiness leading to withdrawal	1/9 (11.1%)	0/12 (0%)	RR 3.9 (0.18 to 85.93)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Number of children with vomiting, sweating and sickness	1/9 (11.1%)	0/12 (0%)	RR 3.9 (0.18 to 85.93)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Number of children with anorexia	1/9 (11.1%)	0/12 (0%)	RR 3.9 (0.18 to 85.93)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Number of children with weight loss	0/57 (0%)	2/57 (3.5%)	RR 0.2 (0.01 to 4.08)	28 fewer per 1000 (from 35 fewer to 108 more)	LOW
Number of children with constipation	3/9 (33.3%)	0/12 (0%)	RR 9.1 (0.53 to 156.72)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

Table 15-24: Low dose imipramine compared to placebo - Clinical summary of findings

Outcome	Low dose imipramine	Placebo	Relative risk (95% CI)	Absolute effect	Quality
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Number of children with anxiety	2/57 (3.5%)	1/57 (1.8%)	RR 2 (0.19 to 21.44)	18 more per 1000 (from 15 fewer to 368 more)	VERY LOW
Number of children with sleep disturbances	5/57 (8.8%)	3/57 (5.3%)	RR 1.67 (0.42 to 6.65)	36 more per 1000 (from 31 fewer to 299 more)	VERY LOW
Number of children with abdominal pain	1/57 (1.8%)	1/57 (1.8%)	RR 1 (0.06 to 15.6)	0 fewer per 1000 (from 17 fewer to 263 more)	VERY LOW
Number of children with weight loss	2/57 (3.5%)	2/57 (3.5%)	RR 1 (0.15 to 6.86)	0 fewer per 1000 (from 30 fewer to 205 more)	VERY LOW

15.2.2.2 *Low dose imipramine compared to high dose imipramine*

One randomised controlled trial, **Martin (1971)**⁹⁸ considered low dose (10 mg) imipramine compared to high dose imipramine (25mg).

Table 15-25: Low dose imipramine compared to high dose imipramine - Clinical summary of findings

Outcome	Low dose imipramine	High dose imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children with anxiety	2/57 (3.5%)	4/57 (7%)	RR 0.5 (0.1 to 2.62)	35 fewer per 1000 (from 63 fewer to 113 more)	VERY LOW
Number of children with sleep disturbances	5/57 (8.8%)	3/57 (5.3%)	RR 1.67 (0.42 to 6.65)	36 more per 1000 (from 31 fewer to 299 more)	VERY LOW
Number of children with abdominal pain	1/57 (1.8%)	1/57 (1.8%)	RR 1 (0.06 to 15.6)	0 fewer per 1000 (from 17 fewer to 263 more)	VERY LOW
Number of children with weight loss	2/57 (3.5%)	0/57 (0%)	RR 5 (0.25 to 101.89)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

15.2.2.3 *Imipramine compared to desmopressin*

One randomised controlled trial, **Vertucci (1997)**¹⁵⁸ considered imipramine compared to desmopressin.

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Table 15-26: Imipramine compared to desmopressin - Clinical summary of findings

Outcome	Imipramine	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children with pallor, restlessness and cold extremities	1/57 (1.8%)	0/57 (0%)	RR 3 (0.12 to 72.13)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

15.2.2.4 Amitriptyline compared to placebo

One randomised controlled trial, **Poussaint (1966)**¹²¹ considered amitriptyline compared to placebo.

Table 15-27: Amitriptyline compared to placebo - Clinical summary of findings

Outcome	Amitriptyline	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who became irritable	7/16 (43.8%)	5/16 (31.3%)	RR 1.4 (0.56 to 3.49)	125 more per 1000 (from 138 fewer to 779 more)	VERY LOW
Number of children who were calmer	2/16 (12.5%)	0/16 (0%)	RR 5 (0.26 to 96.59)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children who were drowsy	3/16 (18.8%)	0/16 (0%)	RR 7 (0.39 to 125.44)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children with fatigue	1/16 (6.3%)	1/16 (6.3%)	RR 1 (0.07 to 14.64)	0 fewer per 1000 (from 59 fewer to 859 more)	VERY LOW
Number of children with stomach ache	1/16 (6.3%)	5/16 (31.3%)	RR 0.2 (0.03 to 1.53)	250 fewer per 1000 (from 304 fewer to 166 more)	VERY LOW
Number of children with lower appetite	1/16 (6.3%)	1/16 (6.3%)	RR 1 (0.07 to 14.64)	0 fewer per 1000 (from 59 fewer to 859 more)	VERY LOW

15.2.2.5 Nortriptyline compared to placebo

One randomised controlled trial, **Lake (1968)**⁸⁷ compared nortriptyline to placebo.

Table 15-28: Nortriptyline compared to placebo - Clinical summary of findings

Outcome	Nortriptyline	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Headache, aching arms and sore tummy	1/54 (1.9%)	0/54 (0%)	RR 3 (0.12 to 72.05)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

15.2.2.6 Imipramine

Two observational studies, **Bain (1973)**⁶ and **Goel (1974)**⁶⁴ considered the side effects of imipramine and amitriptyline.

15.2.2.7 Imipramine compared to placebo for children with bedwetting

One randomised controlled trial, **Tahmaz (2000)**¹⁴⁵ compared imipramine to placebo.

Table 15-29: Imipramine compared to placebo - Clinical summary of findings

Outcome	Imipramine	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children with dry mouth or nausea	3/14 (21.4%)	4/16 (25%)	RR 0.86 (0.23 to 3.19)	35 fewer per 1000 (from 192 fewer to 548 more)	VERY LOW

15.2.2.8 Imipramine compared to oxybutynin for children with bedwetting

One randomised controlled trial, **Tahmaz (2000)**¹⁴⁵ compared imipramine to oxybutynin.

Table 15-30: Imipramine compared to oxybutynin - Clinical summary of findings

Outcome	Imipramine	Oxybutynin	Relative risk (95% CI)	Absolute effect	Quality
Number of children with dry mouth or nausea	3/14 (21.4%)	4/16 (25%)	RR 0.86 (0.23 to 3.19)	35 fewer per 1000 (from 192 fewer to 548 more)	VERY LOW

15.2.2.9 Imipramine compared to imipramine and oxybutynin for children with bedwetting

One randomised controlled trial, **Tahmaz (2000)**¹⁴⁵ compared imipramine to imipramine and oxybutynin.

Table 15-31: Imipramine compared to imipramine and oxybutynin - Clinical summary of findings

Outcome	Imipramine	Imipramine and oxybutynin	Relative risk (95% CI)	Absolute effect	Quality
Number of children with dry mouth or nausea	3/14 (21.4%)	4/23 (17.4%)	RR 1.23 (0.32 to 4.71)	40 more per 1000 (from 118 fewer to 646 more)	VERY LOW

15.2.2.10 Imipramine for children with monosymptomatic nocturnal enuresis

One observational study, **Monda (1995)**¹⁰⁴ considered imipramine for children with monosymptomatic nocturnal enuresis. Children had 1 mg/kg imipramine, increased to 1.5 mg/kg if still wetting after 2 weeks, and was given 30 to 45 minutes before going to bed.

15.2.3 Network Meta-Analysis

Tricyclic medication was amongst the interventions included in a network meta-analysis of interventions used for nocturnal enuresis. The summary of results of this analysis is presented in chapter 24 and a detailed description of the analysis is presented in appendix F. If studies did not meet the inclusion criteria of the network meta-analysis protocol as stated in appendix F they were not included in the network meta-analysis

15.2.4 Health economic evidence review

Given the lack of published evidence assessing the cost-effectiveness of different interventions, including tricyclics, used in the treatment of bedwetting, the GDG identified this area as high priority for original economic analysis. Therefore, a cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK National Health Service and Personal Social Services perspective. The time horizon for the analysis was 13 years, modelling patients from the time they entered at age 7 years until they reached age 20.

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A summary of the analysis is provided below. The full report is presented in appendix G.

Summary of results

The results of the probabilistic sensitivity analysis are summarised in table 15-32 in terms of mean total costs and mean total QALYs and mean net benefit for each treatment sequence, where each mean is the average of 20,000 simulated estimates. The option with the greatest mean net benefit is the most cost-effective at a specified threshold (for example, £20,000). The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

Table 15-32: Basecase probabilistic sensitivity analysis results

Treatment sequence	Mean cost	Mean QALYs	Net Benefit (threshold=£20,000 per QALY)	Probability that strategy is most cost-effective (threshold =£20,000 per QALY)
No Treatment	£0	19.734	£394,684	0.0%
Alarm - Imipramine	£206	19.901	£397,816	0.4%
Imipramine - Desmopressin	£406	19.914	£397,875	0.0%
Imipramine - Desmopressin - Desmopressin+Anticholinergic	£514	19.922	£397,929	0.0%
Desmopressin - Imipramine	£298	19.912	£397,943	0.7%
Imipramine - Alarm - Desmopressin	£374	19.927	£398,169	0.0%
Imipramine - Alarm - Desmopressin - Desmopressin+Anticholinergic	£434	19.932	£398,203	0.0%
Desmopressin - Alarm - Imipramine	£304	19.952	£398,729	0.3%
Alarm - Desmopressin - Imipramine	£275	19.955	£398,814	0.1%
Alarm - Imipramine - Desmopressin	£310	19.959	£398,877	0.0%
Alarm - Imipramine - Desmopressin - Desmopressin+Anticholinergic	£367	19.964	£398,910	0.0%
Desmopressin - Alarm+Desmopressin - Imipramine	£378	19.978	£399,178	3.1%
Desmopressin	£314	19.981	£399,297	7.1%
Alarm - Alarm+Desmopressin - Imipramine	£252	19.981	£399,357	13.1%
Desmopressin - Desmopressin+Anticholinergic	£426	19.990	£399,370	19.8%
Alarm - Desmopressin	£280	19.991	£399,549	4.9%
Desmopressin - Alarm+Desmopressin - Desmopressin	£410	19.998	£399,551	3.3%
Alarm - Desmopressin -	£346	19.997	£399,592	5.6%

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Desmopressin+Anticholinergic				
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£433	20.002	£399,603	3.9%
Desmopressin - Alarm - Desmopressin	£350	19.998	£399,609	7.7%
Alarm - Alarm+Desmopressin - Desmo	£258	19.995	£399,640	15.9%
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£281	19.996	£399,647	8.3%
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£373	20.001	£399,647	5.8%

The results of the incremental analysis in the probabilistic analysis, excluding dominated and extendedly dominated strategies, are presented in table 15-33.

Table 15-33: Incremental analysis of basecase probabilistic results with dominated and extendedly dominated sequences removed

Treatment sequence	Mean cost (£)	Incremental Cost (£)	Mean QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		19.73421		
Alarm - Alarm+Desmopressin - Desmo	£258	£258	19.99489	0.26068	£988
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£282	£24	19.9964	0.00151	£15,828
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£373	£91	20.00099	0.00459	£19,891
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£433	£61	20.00183	0.00084	£72,143

Results of the basecase probabilistic analysis indicate treatment sequences that included imipramine were never cost-effective.

The GDG was concerned that alarms, despite their cost-effectiveness, may not be an appropriate intervention for all children. For this group of children, a strategy of starting and maintaining desmopressin with or without the addition of an anticholinergic until sustained dryness is achieved is considered cost-effective. Imipramine as a first line intervention or as longer term treatment was not cost-effective in this scenario, as desmopressin based strategies were either less costly and more effective (thus dominating imipramine-based sequences) or had a more favourable ICER (thus extendedly dominating imipramine-based sequences).

A series of sensitivity analyses were undertaken to test some of the assumptions feeding into the model and none of these affected the cost-effectiveness of the

sequence alarm followed by combined alarm and desmopressin and then desmopressin alone compared to no treatment. Furthermore, imipramine-based treatment sequences never became cost-effective in any sensitivity analysis undertaken.

The data for imipramine which was fed into the model was not particularly promising, in that the odds ratio of imipramine compared to no treatment from the network meta-analysis crossed 1 and were thus not statistically significant. In addition, despite imipramine's very small acquisition cost, the BNF⁷⁸ states that a consultation with a health care professional must take place every 3 months before further courses of treatment can be pursued. The combination of non-significant effectiveness results and ongoing monitoring costs are likely to contribute to imipramine's poor performance in the cost-effectiveness analysis.

The economic analysis conducted and presented here represents the first undertaken to assess the cost-effectiveness of interventions used in the treatment of children with bedwetting. And although the analysis is directly applicable to decision making in the UK NHS, it has some potentially serious limitations, some of which may significantly impact the overall conclusions that can be drawn. The main limitations of the analysis are related to the fact that assumptions had to be made in the absence of evidence. Some of these key assumptions centre around:

- treatment effectiveness being independent of age
- health care resource use having been estimated by GDG
- utility weights having been estimated by GDG

A full discussion of these can be found in appendix G.

15.2.5 Evidence statements

The evidence statements are organised by population included in studies and intervention. A number of different tricyclic antidepressants drugs have been used in the studies and the GDG wished these to be reported separately.

Studies included children with bedwetting and possible daytime urinary symptoms

Imipramine

The studies included in the review had varying dosages of imipramine given, based on age or weight of the patient, with younger children being given 25 mg imipramine and older children being given 50 mg imipramine.

Agarwala (1968)¹, Hodes (1973)⁷¹, Khorana (1972)⁸², Manhas (1967)⁹⁶, Poussaint (1965)¹²⁰, Smellie (1996)¹⁴⁰

- Six studies showed that children treated with imipramine were more likely to achieve 14 consecutive dry nights compared to children treated with placebo. Relative risk 5.06, 95% CI 2.84, 8.99. Children had an age range of 5 to 16 years and had 2 to 12 weeks of treatment.

Kolvin (1972)⁸³

- One study showed that children treated with imipramine were more likely to have an > 80% improvement in the number of dry nights compared to children treated with placebo. Relative risk 2.47, 95% CI 1.03, 5.89. Children had a mean age of 9 years and 4 months and had 2 months of treatment.
- One study showed that children treated with placebo had 0.52 fewer wet nights per week at follow up compared to children treated with imipramine. Children had a mean age of 9 years and 4 months and had 2 months of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Kolvin (1972)⁸³

- One study showed there was no significant difference in the number of children who had a > 80% improvement in the number of dry nights between children treated with imipramine and children treated with an enuresis alarm. Relative risk 0.86, 95% CI 0.53, 1.4. Children had a mean age of 9 years and 4 months and had 2 months of treatment.
- One study showed that children treated with an enuresis alarm had 1.05 fewer wet nights per week at follow up compared to children treated with imipramine. Children had a mean age of 9 years and 4 months and had 2 months of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

BatIslam (1995)¹⁰, Manhas (1967)⁹⁶

- Two studies showed that children treated with imipramine were more likely to have a >50% improvement in the number of dry nights compared to children treated with placebo. Relative risk 2.35, 95% CI 1.27, 4.34. Children had an age range of 5 to 18 years and had 4 weeks of treatment.

Attenburrow (1984)²

- One study showed there was no significant difference in the number of wet nights per week at the end of treatment between children treated with imipramine and children treated with placebo. Mean difference -2.5, 95% CI -5.74, 0.74. Children had a median age of 7 years and had 7 weeks of treatment.
- One study showed there was no significant difference in the number of wet nights per week at follow up between children treated with imipramine and children treated with placebo. Mean difference -1.5, 95% CI -4.85, 1.85. Children had a median age of 7 years and had 7 weeks of treatment.

Drew (1966)⁴⁴, Fournier (1987)⁶⁰, Harrison (1970)⁷⁰, Kolvin (1972)⁸³, Smellie (1996)¹⁴⁰, Treffert (1964)¹⁴⁹

- Six studies showed that children treated with imipramine had 0.4 to 4 fewer wet nights per week at the end of treatment compared to children treated with placebo. Children had an age range of 5 to 18 years and had 20 nights to 2 months of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Agarwala (1968)¹

- One study showed that children treated with imipramine had fewer wet nights per 2 weeks during treatment compared to children treated with placebo. Mean difference -2.3, 95% CI -4.19, -0.41. Children had an age range of 6 to 12 years and had 2 to 4 weeks of treatment.

Martin (1971)⁹⁸

- One study showed that children treated with imipramine had fewer wet nights during 26 nights of treatment compared to placebo. Mean difference -6.3, 95% CI -8.6, -4. Children had an age range of 5 to 15 years and had 26 nights of treatment. Children had an age range of 5 to 15 years and had 26 nights of treatment.

Harrison (1970)⁷⁰

- Two studies showed there was no significant difference in the number of children who dropped out of the trial between children treated with imipramine and children treated with placebo. Relative risk 5.00 95% CI 0.25, 100.20. Children had an age range of 6 to 18 and had 20 nights.

Vertucci (1997)¹⁵⁸

- One study showed there was no significant difference in the number of children who achieved 14 consecutive dry nights between children treated with imipramine and children treated with desmopressin. Relative risk 0.79, 95% CI 0.59, 1.06. Children had a mean age of 10 years and had 3 weeks of treatment.
- One study showed that children treated with desmopressin had 1.8 fewer wet nights per week at the end of treatment compared to children treated with imipramine. Children had a mean age of 10 years and had 3 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed that children treated with imipramine first had 0.7 fewer wet nights per week after children had been treated with both drugs compared to children treated with desmopressin first. Children had a mean age of 10 years and had 3 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Lee (2005)⁹⁰

- One study showed there was no significant difference in the number of children who had 0 to 1 wet nights per month between children treated with imipramine and children treated with desmopressin. Relative risk 0.35, 95% CI 0.11, 1.13. Children had a mean age of 7.8 years and were treated for 6 months.
- One study showed that children treated with desmopressin had fewer wet nights per week at the end of treatment compared to treatment with imipramine. Mean difference 1.4, 95% CI 0.55, 2.25. Children had a mean age of 7.8 years and were treated for 6 months.
- One study showed there was no significant difference in the number of children who dropped out of the trial between children treated with imipramine and children treated with desmopressin. Relative risk 2.38, 95% CI 0.65, 8.68. Children had a mean age of 7.8 years and were treated for 6 months.
- One study showed children continue to have a decrease in the number of wet nights at 1 month, 3 months and 6 months in treatment with both

imipramine or desmopressin treatment. Children had a mean age of 7.8 years and were treated for 6 months.

- One study showed there was no statistically significant difference in the number of children who had 0 to 1 wet nights per month at the end of treatment between children treated with imipramine and children treated with desmopressin and oxybutinin. Relative risk 0.35, 95% CI 0.11, 1.13. Children had a mean age of 7.8 years and were treated for 6 months.
- One study showed that children treated with desmopressin and oxybutinin had fewer wet nights per week at the end of treatment compared to children treated with imipramine. Mean difference 1.43, 95% CI 0.45, 2.41. Children had a mean age of 7.8 years and were treated for 6 months.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with imipramine and children treated with desmopressin and oxybutinin. Relative risk 2.33, 95% CI 0.64, 8.49. Children had a mean age of 7.8 years and were treated for 6 months.
- One study showed children continue to have a decrease in the number of wet nights at 1 month, 3 months and 6 months in treatment with both imipramine or desmopressin combined with oxybutynin treatment. Children had a mean age of 7.8 years and were treated for 6 months.

Fournier (1987)⁶⁰, Kolvin (1972)⁸³

- Two studies showed that children treated with imipramine had 0 to 0.6 fewer wet nights per week at the end of treatment compared to children treated with an enuresis alarm. Children had a mean age of 8.5 (Fournier 1987) and 9 years and 4 months (Kolvin 1972) and had 6 weeks (Fournier (1987) and 2 months (Kolvin 1972) of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Fournier (1987)⁶⁰

- One study showed there was no difference in the number of children who dropped out of the trial between children treated with imipramine and children treated with an enuresis alarm. Relative risk 1, 95% CI 0.07, 13.37. Children had a mean age of 8.5 and had 6 weeks of treatment.
- One study showed that children treated with imipramine and an enuresis alarm had 0.9 fewer wet nights per week at follow up compared to children treated with imipramine. Children had a mean age of 8 years and 5 months and had 6 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed there was no difference in the number of children who dropped out between children treated with imipramine and children treated with imipramine and an enuresis alarm. There were no drop outs from either treatment group. Children had a mean age of 8 years and 5 months and had 6 weeks of treatment.

Low dose imipramine compared to placebo

One paper considered 10 mg imipramine compared to a placebo. The usual stated dosage for imipramine in the treatment of nocturnal enuresis 25 mg imipramine for younger children and 50 mg imipramine for older children. It was therefore considered that a dosage of 10 mg imipramine should be evaluated separately from the usual higher dosage of imipramine.

Martin (1971)⁹⁸

- One study showed that children treated with 10 mg imipramine had fewer wet nights during 26 nights of treatment compared to children treated with placebo. Mean difference -3.1, 95% CI -5.1, -1.1. Children had an age range of 5 to 15 years and had 26 nights of treatment.
- One study showed that children treated with 25 mg imipramine had fewer wet nights during treatment compared to children treated with 10 mg imipramine. Relative risk 3.2, 95% CI 1.3, 5.1. Children had an age range of 5 to 15 years and had 26 nights of treatment.

Amitriptyline

Poussaint (1966)¹²¹

- One study (containing two trials) showed that children treated with amitriptyline had 1.4 and 1.5 fewer wet nights per week at the end of treatment compared to children treated with placebo. Children had an age range of 5 to 15 years and had treatment for 4 or 8 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Burke (1995)¹⁹

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with amitriptyline and children treated with desmopressin. Relative risk 0.6, 95% CI 0.18, 2.04. Children had a mean age of 8.6 to 8.9 years and had treatment for 16 weeks.

- One study showed there was no statistically significant difference in the mean number of wet nights per week at the end of treatment between children treated with amitriptyline and children treated with desmopressin. Mean difference -1.4, 95% CI -2.95, 0.15. Children had a mean age of 8.6 to 8.9 years and had treatment for 16 weeks.
- One study showed there was no statistically significant difference in the mean number of wet nights per week at follow up between children treated with amitriptyline and children treated with desmopressin. Mean difference 0.1, 95% CI -1.67, 1.87. Children had a mean age of 8.6 to 8.9 years and had treatment for 16 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out of the trial between children treated with amitriptyline and children treated with desmopressin. Relative risk 0.17, 95% CI 0.01, 3.06. Children had a mean age of 8.6 to 8.9 years and had treatment for 16 weeks.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with amitriptyline and children treated with amitriptyline combined with desmopressin. Relative risk 0.6, 95% CI 0.18, 2.04. Children had a mean age of 8.6 to 8.9 years and had treatment for 16 weeks.
- One study showed there was no difference in the mean number of wet nights per week at the end of treatment between children treated with amitriptyline and children treated with amitriptyline combined with desmopressin. Mean difference 0, 95% CI -1.64, 1.64. Children had a mean age of 8.6 to 8.9 years and had treatment for 16 weeks.
- One study showed there was no statistically significant difference in the mean number of wet nights per week at follow up between children treated with amitriptyline and children treated with amitriptyline combined with desmopressin. Mean difference -1.2, 95% CI -3.46, 1.06. Children had a mean age of 8.6 to 8.9 years and had treatment for 16 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out of the trial between children treated with amitriptyline and children treated with amitriptyline combined with desmopressin. Relative risk 0.14, 95% CI 0.01, 2.53. Children had a mean age of 8.6 to 8.9 years and had treatment for 16 weeks.

Danquah (1975)³⁸

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- One study showed that children treated with enuresis alarms had 0.8 fewer wet nights per week compared to children treated with amitriptyline. Children had a mean age of 10.4 years and had treatment for 7 weeks. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed that children treated with an enuresis alarm stopped bedwetting 4.4 days earlier than children treated with amitriptyline. Children had a mean age of 10.4 years and had treatment for 7 weeks.

Nortriptyline compared to placebo

Lake (1968)⁸⁷

- One study showed children treated with nortriptyline had 0.83 fewer wet nights per week during treatment compared to children treated with placebo. Children had an age range of 5 to 12 years and had 2 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Studies included children with bedwetting only Imipramine

Wagner (1982)¹⁶⁰

- For children with bedwetting one study showed there was no significant difference in the number of children who achieved 14 consecutive dry nights between children treated with imipramine and children treated with placebo. Relative risk 4.00, 95 % CI 0.52, 30.76. Children had an age range of 6 to 16 years and had 14 weeks of treatment.

Tahmaz (2000)¹⁴⁵

- One study showed there was no significant difference in the number of children who had 90% improvement in the number of dry nights between children treated with imipramine and children treated with placebo. Relative risk 2.30 95% CI 0.90, 5.86. Children had a mean age of 9.44 years and had 3 months of treatment.
- One study showed there was no significant difference in the number of children who had 50% to 90% improvement in the number of dry nights

between children treated with imipramine and children treated with placebo. Relative risk 1.03, 95% CI 0.42, 2.52. Children had a mean age of 9.44 years and had 3 months of treatment.

- One study showed there was no significant difference in the number of children who relapsed at 6 months between children treated with imipramine and children treated with placebo. Relative risk 1.79, 95% CI 0.55, 5.76. Children had a mean age of 9.44 years and had 3 months of treatment.
- Two studies showed there was no significant difference in the number of children who achieved 50% to 90% improvement in the number of dry nights between children treated with imipramine and children treated with oxybutinin. Relative risk 0.95 95% CI 0.37, 2.45. Children had a mean age of 9.44 years and had 3 months of treatment.
- One study showed there was no significant difference in the number of children who dropped out of the trial between children treated with imipramine and children treated with oxybutynin. Relative risk 0.86 95% CI 0.48, 1.55. Children had a mean age of 9.44 years and had 3 months of treatment.
- One study showed there was no significant difference in the number of children who achieved 50% to 90% improvement in the number of dry nights between children treated with imipramine and children treated with imipramine and oxybutinin. Relative risk 1.43 95% CI 0.53, 3.83. Children had a mean age of 9.44 years and had 3 months of treatment.
- One study showed more children relapsed at 6 months after treatment with imipramine compared to children treated with imipramine and oxybutinin. Relative risk 2.86, 95% CI 1.08, 7.53. Children had a mean age of 9.44 years and had 3 months of treatment.

Lee (2005) ⁹⁰

- One study showed that children treated with desmopressin were more likely to achieve 0 to 1 wet nights per month compared to children treated with imipramine. Relative risk 0.21, 95% CI 0.07, 0.65. Children had a mean age of 7.8 years and were treated for 6 months.
- One study showed that children treated with desmopressin had fewer wet nights per week at the end of treatment compared to children treated with imipramine. Mean difference 1.3, 95% CI 0.38, 2.22. Children had a mean age of 7.8 years and were treated for 6 months.

- One study showed that children treated with desmopressin and oxybutinin were more likely to achieve 0 to 1 wet nights per month compared to children treated with imipramine. Relative risk 0.02, 95% CI 0.07, 0.62. Children had a mean age of 7.8 years and were treated for 6 months.
- One study showed children treated with desmopressin and oxybutinin had fewer wet nights per week at the end of treatment compared to children treated with imipramine. Mean difference 1.07, 95% CI 0.06, 2.08. Children had a mean age of 7.8 years and were treated for 6 months.

Tahmaz (2000)¹⁴⁵, Esmaili (2008)⁵¹

- Two studies showed there was no significant difference in the number of children who achieved 14 consecutive dry nights between children treated with imipramine and children treated with oxybutinin. Relative risk 0.94, 95% CI 0.48, 1.84. Children in Tahmaz (2000) had a mean age of 9.44 years and had 3 months of treatment, children in Esmaili (2008) had a mean age of 8.9 years and had 1 month of treatment.
- Two studies showed there was no significant difference in the number of children who achieved 14 consecutive dry nights between children treated with imipramine and children treated with imipramine and oxybutinin. Relative risk 0.94, 95% CI 0.48, 1.84. Children in Tahmaz (2000) had a mean age of 9.44 years and had 3 months of treatment, children in Esmaili (2008) had a mean age of 8.9 years and had 1 month of treatment.

Esmaili (2008)⁵¹

- One study showed that children treated with oxybutinin had fewer wet nights per week during treatment compared to children treated with imipramine. Mean difference 1, 95% CI 0.02, 1.98. Children had a mean age of 8.9 years and had 1 month of treatment.
- One study showed that children treated with imipramine and oxybutinin had fewer wet nights per week during treatment compared to children treated with imipramine. Mean difference 1, 95% CI 0.02, 1.98. Children had a mean age of 8.9 years and had 1 month of treatment.

Wagner (1982)¹⁶⁰

- One study showed that more children treated with an enuresis alarm achieved 14 consecutive dry nights compared to children treated with

imipramine. Relative risk 0.4, 95% CI 0.17, 0.93. Children had a mean age of 7.9 years and had 14 weeks of treatment.

- One study showed that children treated with an enuresis alarm had 2.17 fewer wet nights per week at the end of treatment compared to children treated with imipramine. Children had a mean age of 7.9 years and had 14 weeks of treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed there was no significant difference in the number of children who relapsed at 6 months between children treated with imipramine and children treated with an enuresis alarm. Relative risk 1.8, 95% CI 0.93, 3.48. Children had a mean age of 7.9 years and had 14 weeks of treatment.

Studies included children with monosymptomatic nocturnal enuresis

Imipramine

Monda (1995) ¹⁰⁴

- One observational study showed 14 out of 44 children with monosymptomatic nocturnal enuresis achieved only 0 to 1 wet nights per month when treated with imipramine. Children had a median age of 9 years and had 6 months of treatment.
- One observational study showed at 12 months follow up 7 out of 44 children with monosymptomatic nocturnal enuresis achieved only 0 to 1 wet nights per month after treatment with imipramine. Children had a median age of 9 years and had 6 months of treatment.

Studies included children with severe bedwetting

Imipramine

Hagglund (1964) ⁶⁷

- For children with severe wetting one study showed there was no significant difference in the number of children who had >90% improvement in the number of dry nights between children treated with imipramine and children treated with placebo. Relative risk 7.88, 95% CI 0.48, 130.28. Children had an age range of 4 to 14 years.

Forsythe (1969)⁵⁹

- For children with severe wetting one study showed there was no significant difference in the number of children who achieved 14 consecutive dry nights between children treated with imipramine and placebo and children treated with placebo. Relative risk 1.12, 95% CI 0.07, 17.57. Children had an age range of up to 15 years and had 8 weeks of treatment.
- For children with severe wetting one study showed there was no significant difference in the number of children who had >50% improvement in the number of dry nights between children treated with imipramine and placebo and children treated with placebo. Relative risk 1.17, 95% CI 0.70, 1.95. Children had an age range of up to 15 years and had 8 weeks of treatment.
- For children with severe wetting one study showed there was no significant difference in the number of children who achieved 14 consecutive dry nights between children treated with imipramine and placebo and children treated with nortriptyline and placebo. Relative risk 1.13, 95% CI 0.07, 17.78. Children had an age range of up to 15 years and had 8 weeks of treatment.
- For children with severe wetting one study showed there was no significant difference in the number of children who had >50% improvement in the number of dry nights between children treated with imipramine and placebo and children treated with nortriptyline and placebo. Relative risk 0.73, 95% CI 0.47, 1.14. Children had an age range of up to 15 years and had 8 weeks of treatment.

Nortriptyline

Forsythe (1969)⁵⁹

- For children with severe wetting one study showed there was no significant difference in the number of children who achieved 14 consecutive dry nights between children treated with nortriptyline and placebo and children treated with placebo. Relative risk 0.99, 95% CI 0.06, 15.55. Children had an age range of up to 15 years and had 8 weeks of treatment.
- For children with severe wetting one study showed children treated with nortriptyline and placebo were more likely to have >50% improvement in the number of dry nights compared to children treated with placebo. Relative risk

1.60, 95% CI 1.02, 2.52. Children had an age range of up to 15 years and had 8 weeks of treatment.

Side effects for tricyclics

The side effects are extracted from RCTs or observational studies and listed by individual tricyclic.

Imipramine

Martin (1971)⁹⁸

- One randomised controlled trial showed there was no statistically significant difference in the number of children with anxiety between children treated with imipramine and children treated with placebo. Relative risk 4, 95% CI 0.46, 34.7. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no difference in the number of children with sleep disturbances between children treated with imipramine and children treated with placebo. Relative risk 1, 95% CI 0.21, 4.75. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no difference in the number of children with weight loss between children treated with imipramine and children treated with placebo. Relative risk 0.20, 95% CI 0.01, 4.08. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with anxiety between children treated with low dose imipramine and children treated with placebo. Relative risk 2, 95% CI 0.19, 21.44. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with sleep disturbances between children treated with low dose imipramine and children treated with placebo. Relative risk 1.67, 95% CI 0.42, 6.65. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no difference in the number of children with abdominal pain between children treated with low

dose imipramine and children treated with placebo. Relative risk 1, 95% CI 0.06, 15.6. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.

- One randomised controlled trial showed there was no difference in the number of children with weight loss between children treated with low dose imipramine and children treated with placebo. Relative risk 1, 95% CI 0.15, 6.86. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.

Attenburrow (1984) ²

- One randomised controlled trial showed there was no statistically significant difference in the number of children with lethargy between children treated with imipramine and children treated with placebo. Relative risk 11.7, 95% CI 0.71, 192.98. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with dizziness and dry mouth between children treated with imipramine and children treated with placebo. Relative risk 3.9, 95% CI 0.18, 85.93. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with upset stomach between children treated with imipramine and children treated with placebo. Relative risk 6.5, 95% CI 0.35, 120.8. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with vomiting and drowsiness leading to withdrawal between children treated with imipramine and children treated with placebo. Relative risk 3.9, 95% CI 0.18, 85.93. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with vomiting, sweating and sickness between children treated with imipramine and children treated with placebo. Relative risk 3.9, 95% CI 0.18, 85.93. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.

- One randomised controlled trial showed there was no statistically significant difference in the number of children with anorexia between children treated with imipramine and children treated with placebo. Relative risk 3.9, 95% CI 0.18, 85.93. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with constipation between children treated with imipramine and children treated with placebo. Relative risk 9.1, 95% CI 0.53, 156.72. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.

Agarwala (1968) ¹

- One randomised controlled trial showed there was no statistically significant difference in the number of children with dizziness between children treated with imipramine and children treated with placebo. Relative risk 3, 95% CI 0.13, 70.74. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.

Manhas (1967) ⁹⁶

- One randomised controlled trial showed there was no statistically significant difference in the number of children with giddiness between children treated with imipramine and children treated with placebo. Relative risk 1.86, 95% CI 0.18, 19.38. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with abdominal pain and epitaxis between children treated with imipramine and children treated with placebo. Relative risk 2.8, 95% CI 0.12, 65.93. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.

Manhas (1967) ⁹⁶, Martin (1971) ⁹⁸

- Two randomised controlled trials showed there was no statistically significant difference in the number of children with abdominal pain between children treated with imipramine and children treated with placebo. Relative risk 2.89, 95% CI 0.46, 18.13. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.

Batislam (1995) ¹⁰

- One randomised controlled trial showed there was no statistically significant difference in the number of children with gastrointestinal problems between children treated with imipramine and children treated with placebo. Relative risk 13, 95% CI 0.82, 205.24. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.

Vertucci (1997) ¹⁵⁸

- One randomised controlled trial showed there was no statistically significant difference in the number of children with pallor, restlessness and cold extremities between children treated with imipramine and children treated with desmopressin. Relative risk 3, 95% CI 0.12, 72.13. Children had a mean age of 10 years and had 3 weeks of treatment.

Bain (1973) ⁶

- One observational trial showed there was an increase in cases of imipramine poisoning, in 1968 and 1970, in 1968 17 cases of poisoning were reported, by 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 died from nocturnal enuresis.

Goel (1974) ⁶⁴

- One observational trial showed there were 60 cases of amitriptyline and imipramine poisoning in children between January 1966 and July 1973. 16 of which were from the medication prescribed for the child poisoned for 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, 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 ataxia, 5 had mydriasis, 9 had vomiting, 8 had flushing of the face, 1 had coma, 6 had convulsions, 4 had hyperreflexia,

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 ataxia, 8 had mydriasis, 3 had vomiting, 3 had flushing of the face, 2 had coma, 2 had convulsions, 1 had hyperreflexia, 2 had retention of urine, 0 had hallucinations, 1 had dysarthria and 0 had nystagmus.

Tahmaz (2000) ¹⁴⁵

- One randomised controlled trial showed there was no statistically significant difference in the number of children with dry mouth or nausea between children treated with imipramine and children treated with placebo. Relative risk 0.86, 95% CI 0.23, 3.19. Children had a mean age of 9.44 years and had 3 months of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with dry mouth or nausea between children treated with imipramine and children treated with oxybutynin. Relative risk 0.86, 95% CI 0.23, 3.19. Children had a mean age of 9.44 years and had 3 months of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with dry mouth or nausea between children treated with imipramine and children treated with imipramine and oxybutynin. Relative risk 1.23, 95% CI 0.32, 4.71. Children had a mean age of 9.44 years and had 3 months of treatment.

Monda (1995) ¹⁰⁴

- One observational study showed 3 out of 44 children reported hyperactivity while treated with imipramine. Children had a median age of 9 years and had 6 months of treatment.

Low dose imipramine compared to high dose imipramine

Martin (1971) ⁹⁸

- One randomised controlled trial showed there was no statistically significant difference in the number of children with anxiety between children treated with low dose imipramine and children treated with high dose imipramine. Relative risk 2, 95% CI 0.19, 21.44. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.

- One randomised controlled trial showed there was no statistically significant difference in the number of children with sleep disturbances between children treated with low dose imipramine and children treated with high dose imipramine. Relative risk 1.67, 95% CI 0.42, 6.65. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no difference in the number of children with abdominal pain between children treated with low dose imipramine and children treated with high dose imipramine. Relative risk 1, 95% CI 0.06, 15.6. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.
- One randomised controlled trial showed there was no difference in the number of children with weight loss between children treated with low dose imipramine and children treated with high dose imipramine. Relative risk 1, 95% CI 0.15, 6.86. Children had an age range of 5 to 18 years and had between 20 nights and 3 months of treatment.

Amitriptyline

Poussaint (1966)¹²¹

- One randomised controlled trial showed there was no statistically significant difference in the number of children who became irritable between children treated with amitriptyline and children treated with placebo. Relative risk 1.4, 95% CI 0.56, 3.49. Children had an age range of 5 to 15 years and had 4 weeks of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children who became calmer between children treated with amitriptyline and children treated with placebo. Relative risk 5, 95% CI 0.26, 96.59. Children had an age range of 5 to 15 years and had 4 weeks of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children who became drowsy between children treated with amitriptyline and children treated with placebo. Relative risk 7, 95% CI 0.39, 125.44. Children had an age range of 5 to 15 years and had 4 weeks of treatment.
- One randomised controlled trial showed there was no difference in the number of children who had fatigue between children treated with

amitriptyline and children treated with placebo. Relative risk 1, 95% CI 0.07, 14.64. Children had an age range of 5 to 15 years and had 4 weeks of treatment.

- One randomised controlled trial showed there was no statistically significant difference in the number of children who had stomach ache between children treated with amitriptyline and children treated with placebo. Relative risk 0.2, 95% CI 0.03, 1.53. Children had an age range of 5 to 15 years and had 4 weeks of treatment.
- One randomised controlled trial showed there was no difference in the number of children who had a lower appetite between children treated with amitriptyline and children treated with placebo. Relative risk 1, 95% CI 0.07, 14.64. Children had an age range of 5 to 15 years and had 4 weeks of treatment.

Nortriptyline

Lake (1968)⁸⁷

One randomised controlled trial showed there was no statistically significant difference in the number of children with a sore tummy between children treated with nortriptyline and children treated with placebo. Relative risk 3, 95% CI 0.12, 72.05. Children had an age range of 5 to 15 years and had 2 weeks of treatment.

NCGC network meta-analysis (see appendix F)

For children with bedwetting and possible day time symptoms

- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with imipramine and no treatment / placebo. Relative risk 6.149, 95% CI 3.100, 8.537. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**
- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with amitriptyline and no treatment / placebo. Relative risk 9.514, 95% CI 6.906, 9.677. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**

For children with bedwetting only

- **The NCGC NMA showed there was no statistically significant difference in the number of children who experienced a recurrence of bedwetting at 6 months between children treated with combined imipramine and oxybutynin and no treatment / placebo. Relative risk**

0.011, 95% CI 0.0001, 2.764. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.

- **The NCGC NMA showed there was no statistically significant difference in the number of children who experienced a recurrence of bedwetting at 6 months between children treated with imipramine and no treatment / placebo. Relative risk 4.566, 95% CI 0.277, 52.54. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**
- **The NCGC NMA showed there was no statistically significant difference in the number of children who achieved a full response between children treated with imipramine and no treatment / placebo. Relative risk 2.259, 95% CI 0.513, 6.172. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**
- **The NCGC NMA showed there was no statistically significant difference in the number of children who achieved a full response between children treated with combined imipramine and oxybutynin and no treatment / placebo. Relative risk 4.188, 95% CI 0.561, 8.737. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**

For estimates of treatment effect relative to other active comparators, please see section 24.4 in chapter 24.

15.2.6 Health economic evidence statements

NCGC economic evaluation (see appendix G)

- **Intervention sequences that include imipramine are not cost-effective in the treatment of children with bedwetting as they are more costly and less effective than alternative intervention sequences such as ones starting with alarm and moving to combined alarm and desmopressin or starting with desmopressin and moving on the alarm or combined desmopressin and anticholinergic. This evidence has potentially serious limitations and direct applicability.**

15.2.7 Evidence to recommendations

Relative values of different outcomes

The GDG considered the children and parents or carers starting treatment for bedwetting were seeking an outcome of sustained dryness. A number of different outcomes were used to capture this: the outcome of 14 consecutive dry nights, reduction in wet nights and the mean number of wet nights allow evaluation of the effectiveness of treatment. Follow up rates indicate where available can indicate sustained dryness.

Trade off between clinical benefit and harms

The GDG were concerned about the potential side effects of tricyclic antidepressants and their danger in overdose.

Economic considerations

Imipramine was shown not to be a cost-effective first-line intervention for the treatment of bedwetting. First line treatment with alarm or desmopressin is likely to be less costly and more effective than offering imipramine.

Imipramine is not considered to be a cost-effective intervention and therefore should not be used early in the treatment of bedwetting. If, however, patients have not responded to any other treatments or they are deemed unsuitable for various reasons, imipramine could be considered as a possible alternative.

Quality of evidence (this includes clinical and economic)

The evidence from studies of direct comparisons was generally poor with many older studies which had wide confidence intervals which lacked follow up data. There were questions over the lengths of treatment for both imipramine, which may take longer to be effective than other drug treatments and for enuresis alarm comparisons where the length of treatment was insufficient to see the full effect of the treatment.

Other considerations

The GDG used the evidence from direct comparisons, the network meta-analysis and the health economic evidence to inform their recommendations.

While the research studies have used various tricyclic antidepressants the GDG considered that imipramine was the tricyclic of choice to use in children. It is the drug most commonly used for this indication and there is therefore more experience of its use and the case fatality rate is considered to be higher with other tricyclics.

One study used a lower dose of imipramine (10mg) than currently recommended and although 25mg was more effective, the lower dose did results in fewer wet nights compared to placebo. This might indicate that lower doses are worth trying if imipramine is being used.

The GDG considered that from clinical experience there was a role for the use of tricyclic antidepressants, particularly for children with daytime symptoms, although some children with bedwetting only do also respond.

The GDG considered children and families required information to understand the use of imipramine and developed a recommendation on information for children and families from professional and personal experience.

The GDG considered however that a trial of imipramine should only be instigated by healthcare professionals with appropriate expertise in using imipramine. The GDG considered that children started on imipramine require careful follow up and review because of the side effect profile to ensure that children are only continuing to take the drug if it is effective. Imipramine should be slowly withdrawn if side effects are experienced or if there is no improvement in bedwetting after 2 weeks at maximum dose for age.

Children who respond well require medical follow up at 3 monthly intervals along with slow withdrawal of medication ensuring that the dose of imipramine is kept as low as possible to maintain dryness.

15.2.8 Recommendations

- 15.2.8.1 *Do not use tricyclic antidepressants as a first-line treatment for bedwetting in children. [1.13.1]*
- 15.2.8.2 *If offering a tricyclic antidepressant, imipramine¹¹ should be used for the treatment of bedwetting in children.[1.13.2]*
- 15.2.8.3 *Consider imipramine for children with bedwetting who:*
- *have not responded to all other treatments **and***
 - *have been assessed by a healthcare professional with expertise in the management of bedwetting that has not responded to an alarm and/or desmopressin.[1.13.3]*
- 15.2.8.4 *If offering imipramine for bedwetting in children, inform the child and parents or carers:*
- *that many children, but not all, will experience a reduction in wetness*
 - *how imipramine works*
 - *that it should be taken before bedtime*
 - *that the dose should be increased gradually*
 - *about relapse rates(for example, more than two out of three children will relapse after a 3-month course of imipramine)*
 - *that the initial treatment course is for 3 months and further courses may be considered*
 - *about the particular dangers of imipramine overdose, and the importance of taking only the prescribed amount and storing it safely.[1.13.4]*
- 15.2.8.5 *Perform a medical review every 3 months in children who are using repeated courses of imipramine for the management of bedwetting.[1.13.5]*
- 15.2.8.6 *Withdraw imipramine gradually when stopping treatment for bedwetting in children.[1.13.6]*

¹¹ Imipramine is currently not licensed for use in children under the age of 7 years.

16 Dose escalation in the management of bedwetting

16.1 Introduction

This section presents the evidence outlining the effectiveness of dose escalation in drug treatment of bedwetting. The important question for the health care professional and patient is whether it is useful to increase the dose of medication if the patient has not responded to the initial dose. This review considers the cost and clinical effectiveness of increasing the dose of a drug if the patient has not responded to an initial lower dose.

No evidence was found on the effectiveness of increasing the dose of tricyclics or anticholinergics; the evidence for dose escalation of desmopressin is presented below.

16.2 *What is the clinical and cost effectiveness of dose escalation for children and young people under 19 years who have bedwetting*

16.2.1 Evidence review

16.2.1.1 *Dose escalation of tablet desmopressin for treatment resistant children with bedwetting only.*

One randomised controlled trial, **Schulman (2001)**¹³⁶ compared increasing doses of tablet desmopressin in children who had not responded to lower doses to a matching placebo regime. **Schulman (2001)**¹³⁶ considered treatment resistant children with bedwetting only. The trial included 148 patients who had previously been treated in a trial and received 200 micrograms, 400 micrograms, 600 micrograms or placebo and had 3 or more wet nights during a 2 week washout at the end of the trial. The patients were then randomised to groups to receive desmopressin or placebo. In the desmopressin group the patients received 200 micrograms tablet desmopressin for 2 weeks; after this time if they had not improved their dose was increased to 400 micrograms for 2 weeks; if the patient did not improve again the treatment was increased to 600 micrograms for 2 weeks. The placebo group received matching placebo with the same regime.

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Table 16-1: Increasing desmopressin compared to placebo - Clinical summary of findings

Outcome	Desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who required full dosage of 600 micrograms desmopressin	86/99 (86.9%)	38/38 (100%)	RR 0.88 (0.8 to 0.95)	120 fewer per 1000 (from 50 fewer to 200 fewer)	MODERATE
Number of children who only required 200 micrograms desmopressin	1/99 (1%)	0/38 (0%)	RR 1.17 (0.05 to 28.11)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Number of children who only required 400 micrograms desmopressin	3/99 (3%)	0/38 (0%)	RR 9.75 (0.59 to 160.72)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children who achieved over 50% reduction in number of wet nights	51/99 (51.5%)	4/35 (11.4%)	RR 2.58 (1.29 to 5.13)	180 more per 1000 (from 33 more to 471 more)	LOW
Mean number of wet nights in first 2 of treatment	109	38	-	MD -1 (-1.57 to -0.43)	LOW
Mean number of wet nights in last 2 weeks of treatment	99	38	-	MD -1.3 (-1.88 to -0.72)	MODERATE
Number of children who had dropped out by end of trial	11/99 (11.1%)	0/38 (0%)	RR 8.97 (0.54 to 148.57)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

16.2.1.2 Dose escalation of tablet desmopressin for treatment resistant children with monosymptomatic nocturnal enuresis

One observational study, **Matthiesen (1994)**⁹⁹ considered increasing doses of tablet desmopressin in children who had not responded to lower doses. **Matthiesen (1994)**⁹⁹ considered children with monosymptomatic nocturnal enuresis. The study conducted a 2 week dose titration, 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 the patient was not dry for the whole week the dose was increased to 400 micrograms tablet desmopressin for one week.

NOCTURNAL ENURESIS: FINAL VERSION

16.2.2 Health economic evidence review

Given the lack of published evidence assessing the cost-effectiveness of different interventions used in the treatment of bedwetting, the GDG identified this area as high priority for original economic analysis. Therefore, a cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK National Health Service and Personal Social Services perspective. The analysis set out to evaluate the comparative cost-effectiveness of different intervention sequences used in the treatment of bedwetting in children. Intervention sequences comprised of different permutations of alarm, imipramine, desmopressin, combined alarm and desmopressin and combined alarm and anticholinergic.

A summary of the analysis is provided below. The full report is presented in appendix G.

Dose escalation of desmopressin in the model

The cost of desmopressin was been calculated to reflect the average cost of desmopressin for the treatment of bedwetting. Based on dose-escalation studies identified in the clinical review, some patients will respond to initial low doses of desmopressin, but many will need to increase their dose in order to see a response. Schulman¹³⁶ showed that 99 percent of patients receiving desmopressin would reach 400 micrograms, the maximum dose licensed for the treatment of bedwetting in the BNF⁷⁸. In the base case analysis, 75 percent of modelled patients were assumed to require the maximum dose (400 micrograms), whilst the other 25 percent required the lower, starting dose (200 micrograms). This more conservative estimate of dose escalation was based upon the clinical experience of the GDG. However, the effect of this conservative assumption was explored in a sensitivity analysis reflecting the results of Schulman and colleagues where 100% of patients were assumed to increase to the higher dosage.

Summary of results

Results of the basecase probabilistic analysis are presented in the health economic evidence review for desmopressin (section 13.2.3). The GDG considered that the differences between intervention sequences were relatively small and the probabilistic results indicated substantial uncertainty around the mean cost and benefit estimates. Small changes to the model inputs appears to result in substantial changes to the conclusions about modelled sequences' relative and overall cost-effectiveness.

In the sensitivity analysis, increasing the dose of desmopressin results in an increase in overall costs and thus an increase in the incremental cost-effectiveness ratio of

treatment sequences starting with desmopressin compared to sequences starting with alarm. When 75% of children require the higher dose, desmopressin as an initial strategy may be cost-effective compared to alarm. If 100% of children require the higher dose, desmopressin as an initial strategy is less likely to be cost-effective compared to alarm.

The GDG was concerned that alarms, despite their cost-effectiveness, may not be an appropriate intervention for all children. For this group of children, a strategy of starting and maintaining desmopressin with or without the addition of an anticholinergic until sustained dryness is achieved is considered cost-effective. This is true regardless of the proportion of children requiring higher doses of desmopressin.

A full discussion of these can be found in appendix G.

16.2.3 Evidence statements

Studies included children with bedwetting only

Dose escalation of tablet desmopressin

Schulman (2001)¹³⁶

- One study showed more children treated with placebo required the maximum dosage increase compared to children treated with tablet desmopressin (starting at 200 micrograms increasing to 400 micrograms or 600 micrograms if no response to lower doses). Relative risk 0.88, 95% CI 0.80, 0.95. Children had an age range of 5 to 14 years and treatment length was for 8 weeks.
- One study showed all (38 out of 38) children in the placebo group required the full dosage compared to 86 out of 99 children in the desmopressin group. Children had an age range of 5 to 14 years and treatment length was for 8 weeks.
- One study showed there was no statistically significant difference in the number of children who only required the first dose of desmopressin (200 micrograms) or placebo. Relative risk 1.17, 95% CI 0.05, 28.11. One out of 99 children in the desmopressin group only required 200 micrograms desmopressin, all children in the placebo group required the full dosage increase. Children had an age range of 5 to 14 years and treatment length was for 8 weeks.

- One study showed there was no statistically significant difference in the number of children who only required the second dose of desmopressin (400 micrograms) or placebo. Relative risk 9.75, 95% CI 0.59, 160.72. Three out of 99 children in the desmopressin group required 0.4 mg desmopressin, all children in the placebo group required the full dosage increase. Children had an age range of 5 to 14 years and treatment length was for 8 weeks.
- One study showed children treated with desmopressin were more likely to achieve a greater than 50% reduction in the number of wet nights compared to children treated with placebo. Relative risk 2.58, 95% CI 1.29, 5.13. Twenty-eight children achieved this while being treated with 200 micrograms desmopressin, 16 while being treated with 400 micrograms desmopressin and 8 while being treated with 600 micrograms desmopressin. 47 children never achieved a greater than 50% improvement in the number of dry nights. Children had an age range of 5 to 14 years and treatment length was for 8 weeks.
- One study showed that children treated with tablet desmopressin starting at 200 micrograms increasing to 400 micrograms or 600 micrograms if no response to lower doses had fewer wet nights in the first 2 weeks of treatment compared to those who were treated with placebo. Mean difference -1, 95% CI -1.57, -0.43. Children had an age range of 5 to 14 years and treatment length was for 8 weeks.
- One study showed that children treated with tablet desmopressin starting at 200 micrograms increasing to 400 micrograms or 600 micrograms if no response to lower doses had fewer wet nights in the last 2 weeks of treatment compared to those who were treated with placebo. Mean difference -1.3, 95% CI -1.88, -0.72. Children had an age range of 5 to 14 years and treatment length was for 8 weeks.
- One study showed there was no statistically significant difference in the number of children who had dropped out between the children treated with tablet desmopressin starting at 200 micrograms increasing to 400 micrograms or 600 micrograms if no response to lower doses and those treated with placebo. Relative risk 8.97, 95% CI 0.54, 148.57. Children had an age range of 5 to 14 years and treatment length was for 8 weeks.

Studies included children with mono-symptomatic nocturnal enuresis

Dose escalation of tablet desmopressin

Matthiesen (1994)⁹⁹

- One observational study showed 5 children out of 33 became dry while treated with 200 micrograms tablet desmopressin for 1 week. 26 children then had their dosage increased to 400 micrograms tablet desmopressin for 1 week, during this time 2 children became dry. Children had a mean age of 11.6 (sd 3) years and had 2 weeks of treatment.
- One observational study showed during the week where children were given 200 micrograms tablet desmopressin 2 children dropped out. During the following week where children were given 400 micrograms tablet desmopressin another 2 children dropped out. Children had a mean age of 11.6 (sd 3) years and had 2 weeks of treatment.

16.2.4 Health economic evidence statements

NCGC economic evaluation

Increasing the dose of desmopressin results in an increase in overall costs and thus an increase in the incremental cost-effectiveness ratio of treatment sequences starting with desmopressin compared to sequences starting with alarm. When 75% of children require the higher dose, desmopressin as an initial strategy may be cost-effective compared to alarm. If 100% of children require the higher dose, desmopressin as an initial strategy is unlikely to be cost-effective unless alarms are unsuitable. This evidence has potentially serious limitations and direct applicability.

16.2.5 Evidence to recommendations

Relative values of different outcomes

In comparing dose escalation it is important to consider if increasing the dose meant more patients became dry or drier, both 14 consecutive dry nights and having more dry nights was important as the dose was increased.

Trade off between clinical benefit and harms

No evidence of harms from the RCTs of increasing the dose of tablet desmopressin

Economic considerations

Original modeling undertaken for the guideline evaluated the impact of low dose and high dose desmopressin on the overall cost of treatment strategies involving desmopressin. Increasing the dose of desmopressin increases the cost of treatment and thus the incremental cost-effectiveness ratios of intervention sequences starting with desmopressin compared to those starting with alarms. The basecase analysis showed that if 75% of children were increased to a maximum dosage of desmopressin, it may be considered a cost-effective treatment. If 100% of children required a maximum dose, then a treatment sequence starting with desmopressin

would likely be less cost-effective. The analysis as a whole showed that there was considerable uncertainty about which intervention was the most cost-effective first line option. The GDG considered that first line treatment with alarm is likely to be less costly than first line treatment with desmopressin, and this is true regardless of the dose prescribed.

Quality of evidence (this includes clinical and economic)

Low quality evidence of one RCT with wide confidence intervals and one observational trial

Other considerations

The clinical experience of the GDG was that children a significant proportion of children will require the higher dose of desmopressin. This is in keeping with the trial data that indicated that 86% of children in the desmopressin arm required titration to the higher dose in the trial (400 micrograms or 600 micrograms) . The UK product licence is however up to 400microg, and study allowed titration up to 600microg. Most children had a partial response with the lower dose.

16.2.6 Recommendations

16.2.6.1 In children who have failed to achieve complete dryness after 1 to 2 weeks on the initial dose of desmopressin (200 micrograms for Desmotabs and 120 micrograms for DesmoMelt), consider dose escalation (to 400 micrograms of Desmotabs and 240 micrograms of DesmoMelt).[1.10.3]

17 Treatment for children who do not respond to initial treatment with desmopressin and / or enuresis alarms for the management of bedwetting

17.1 Introduction

This section presents the evidence outlining which treatment should be considered when children have not responded to first line treatment. The question for the health care professional and patient is – should I continue with the treatment I have tried already or should I try an alternative treatment and if so what treatment should I use?

The evidence review indicated that multiple combinations of first line and second line treatments have been studied. Many children do not respond to first line treatment and the GDG were keen to understand the available evidence and how it might inform recommendations and practice. The tables below present the available evidence according to which treatment the child had not responded to and which treatment was used next.

The GDG considered from the direct evidence, the network meta-analysis, the health economic evidence and their clinical experience that alarms or desmopressin were the first line treatments of choice. Tricyclic antidepressants did not emerge from the analyses as optimal first line treatments. Although studies examining treatment after non-response to tricyclic antidepressants were extracted and initially included in the evidence review details are not reported in this chapter as the GDG did not consider tricyclics should be used first line.

17.2 *What is the clinical and cost effectiveness of additional treatment in children who have not responded to an adequate trial of desmopressin and / or enuresis alarms*

17.2.1 Evidence review

Children who have not responded to ENURESIS ALARM therapy

17.2.1.1 Enuresis alarm compared to modified dry bed training (with an enuresis alarm) for children who have not responded to enuresis alarm therapy

Two randomised controlled trials, **Butler (1988)**²⁴ and **Butler (1990)**²⁶, compared enuresis alarms to modified dry bed training with an enuresis alarm in children who have not responded to enuresis alarm treatment. **Butler (1988)**²⁴ and **Butler (1990)**²⁶ described modified dry bed training as a waking schedule, retention control training, positive practice and cleanliness training but without any reprimands (adapted from Azrin (1974)⁴).

Table 17-1: Enuresis alarm compared to DBT for children who have not responded to enuresis alarms - Clinical summary of findings

Outcome	Alarm	DBT	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	40/52 (76.9%)	29/59 (49.2%)	RR 1.52 (1.14 to 2.04)	256 more per 1000 (from 69 more to 512 more)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	52	59	-	not pooled	VERY LOW
Number of children who relapsed	17/48 (35.4%)	13/49 (26.5%)	RR 1.14 (0.63 to 2.07)	37 more per 1000 (from 98 fewer to 284 more)	VERY LOW
Number of children who dropped out	1/24 (4.2%)	2/24 (8.3%)	RR 0.5 (0.05 to 5.15)	42 fewer per 1000 (from 79 fewer to 344 more)	VERY LOW

17.2.1.2 Desmopressin compared to placebo for children who have not responded to enuresis alarm therapy

One randomised controlled trial **Dimson (1996)**⁴² compared 20 µg intranasal desmopressin to placebo in children who had not responded to enuresis alarm treatment.

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Table 17 -2: Desmopressin compared to placebo for children who have not responded to enuresis alarms - Clinical summary of findings

Outcome	Desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	2/17 (11.8%)	0/17 (0%)	RR 5 (0.26 to 97)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	17	17	-	not pooled	VERY LOW
Number of children who relapsed	2/2 (100%)	0/0 (0%)	not pooled	not pooled	LOW

Children who have not responded to DESMOPRESSIN

17.2.1.3 *Enuresis alarm and placebo compared to enuresis alarm and desmopressin for children who have not responded to desmopressin therapy*

One randomised controlled trial, **Gibb (2003)**⁶³, compared enuresis alarm and placebo to enuresis alarm with 20 - 40 µg intranasal desmopressin in children who had not responded to desmopressin.

Table 17-3: Enuresis alarm and placebo compared to enuresis alarm and desmopressin for children who have not responded to enuresis alarm or desmopressin - Clinical summary of findings

Outcome	Alarm and placebo	Alarm and desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 28 consecutive dry nights	51/106 (48.1%)	52/101 (51.5%)	RR 0.93 (0.71 to 1.23)	36 fewer per 1000 (from 149 fewer to 118 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	106	101	-	MD 0.6 (0.23 to 0.97)	VERY LOW

Number of children who dropped out	17/106 (16%)	9/101 (8.9%)	RR 1.8 (0.84 to 3.85)	71 more per 1000 (from 14 fewer to 254 more)	VERY LOW
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Children who have not responded to DESMOPRESSIN, IMIPRAMINE OR OXYBUTYNIN therapy

17.2.1.4 *Acupuncture for children who had not responded to desmopressin, imipramine or oxybutynin*

One observational study **Serel (2001)**¹³⁷ considered acupuncture for children who had not responded to treatment with desmopressin, imipramine or oxybutynin. The study was identified in the update search.

Children with severe wetting resistant to ENURESIS ALARM therapy

17.2.1.5 *Desmopressin compared to placebo for children with severe wetting resistant to enuresis alarm therapy*

One randomised controlled trial **Terho (1991)**¹⁴⁷ compared 20 to 40 µg intranasal desmopressin to placebo in children who had not responded to enuresis alarm treatment.

Table 17-4: Desmopressin compared to placebo for children with severe wetting resistant to enuresis alarms - Clinical summary of findings

Outcome	Desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment (no sd)	26	26	-	not pooled	LOW

Children who have not responded to ENURESIS ALARM therapy or DESMOPRESSIN

17.2.1.6 *Desmopressin compared to placebo for children with bedwetting for children who have not responded to enuresis alarm or desmopressin therapy*

Two randomised controlled trials, **Fjellestad (1987)**⁵⁸ and **Stenberg (1994)**¹⁴¹ compared desmopressin to placebo for children who have not responded to enuresis

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alarms or desmopressin. **Fjellestad (1987)**⁵⁸ considered 200 µg tablet and 20 µg intranasal desmopressin to placebo and **Stenberg (1994)**¹⁴¹ considered 200 to 400 µg tablet desmopressin to placebo.

Table 17-5: Desmopressin tablets compared to placebo for children with bedwetting who have not responded to enuresis alarms or desmopressin - Clinical summary of findings

Outcome	Desmopressin tablets	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	2/30 (6.7%)	0/30 (0%)	RR 5 (0.25 to 99.95)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Mean number of wet nights per week at the end of treatment	10	10	-	MD -2.3 (-3.57 to -1.03)	LOW
Mean number of wet nights per week at the end of treatment (no sd)	30	30	-	not pooled	VERY LOW

Table 17-6: Desmopressin spray compared to placebo for children with bedwetting resistant to enuresis alarms or desmopressin - Clinical summary of findings

Outcome	Desmopressin spray	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	1/30 (3.3%)	0/30 (0%)	RR 3 (0.13 to 70.83)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	30	30	-	not pooled	VERY LOW

17.2.1.7 *Tablet desmopressin compared to intranasal desmopressin for children with bedwetting for children who have not responded to enuresis alarm or desmopressin therapy*

One randomised controlled trial **Fjellestad (1987)**⁵⁸ compared 200 µg tablet desmopressin to 20 µg intranasal desmopressin for children who have not responded to enuresis alarms or desmopressin.

Table 17-7: Tablet desmopressin compared to intranasal desmopressin for children with bedwetting who have not responded to enuresis alarms or desmopressin - Clinical summary of findings

Outcome	Tablet desmopressin	Intranasal desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	2/30 (6.7%)	1/30 (3.3%)	RR 2 (0.19 to 20.9)	33 more per 1000 (from 27 fewer to 657 more)	VERY LOW
Mean number of wet nights per week at the end of treatment (no sd)	30	30	-	not pooled	VERY LOW

Children who have not responded to ENURESIS ALARM therapy and DESMOPRESSIN

17.2.1.8 *Imipramine compared to placebo for children with bedwetting for children who have not responded to enuresis alarm and desmopressin therapy*

One randomised controlled trial **Neveus (2008)**¹¹³ compared 25 to 50mg imipramine to placebo for children who have not responded to enuresis alarms and desmopressin.

Table 17 -8: Imipramine compared to placebo for children with bedwetting who have not responded to enuresis alarms and desmopressin - Clinical summary of findings

Outcome	Imipramine	Placebo	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who achieved 14 consecutive dry nights	5/25 (20%)	0/25 (0%)	RR 11 (0.64 to 188.95)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children who achieved >50% improvement	2/25 (8%)	0/25 (0%)	RR 5 (0.25 to 99.16)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Mean number of wet nights in the last 2 weeks of treatment	25	25	-	MD -3.2 (-5.72 to -0.68)	LOW
Number of children who dropped out	1/25 (4%)	1/25 (4%)	RR 1 (0.07 to 15.12)	0 fewer per 1000 (from 37 fewer to 565 more)	LOW

17.2.1.9 *Imipramine compared to tolterodine for children with bedwetting for children who have not responded to enuresis alarm and desmopressin therapy*

One randomised controlled trial **Neveus (2008)**¹¹³ compared 25 to 50mg imipramine to 1 to 2 mg tolterodine for children who have not responded to enuresis alarms and desmopressin.

Table 17 -9: Imipramine compared to tolterodine for children with bedwetting who have not responded to enuresis alarms and desmopressin - Clinical summary of findings

Outcome	Imipramine	Tolterodine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	5/25 (20%)	0/25 (0%)	RR 11 (0.64 to 188.95)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children who achieved >50% improvement	2/25 (8%)	1/25 (4%)	RR 2 (0.19 to 20.67)	40 more per 1000 (from 32 fewer to 787 more)	LOW
Mean number of wet nights in the last 2 weeks of treatment	25	25	-	MD -2.6 (-5.12 to -0.08)	LOW
Number of children who dropped out	1/25 (4%)	0/25 (0%)	RR 3 (0.13 to 70.3)	0 more per 1000 (from 0 fewer to 0 more)	LOW

17.2.1.10 *Tolterodine compared to placebo for children with bedwetting for children who have not responded to enuresis alarm and desmopressin therapy*

One randomised controlled trial **Neveus (2008)**¹¹³ compared 1 to 2 mg tolterodine to placebo for children who have not responded to enuresis alarms and desmopressin.

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Table 17 -10: Tolterodine compared to placebo for children with bedwetting who have not responded to enuresis alarms and desmopressin - Clinical summary of findings

Outcome	Tolterodine	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	0/25 (0%)	0/25 (0%)	not pooled	not pooled	MODERATE
Number of children who achieved >50% improvement	1/25 (4%)	0/25 (0%)	RR 3 (0.13 to 70.3)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Mean number of wet nights in the last 2 weeks of treatment	25	25	-	MD -0.6 (-2.76 to 1.56)	LOW
Number of children who dropped out	0/25 (0%)	1/25 (4%)	RR 0.33 (0.01 to 7.81)	27 fewer per 1000 (from 40 fewer to 272 more)	LOW

Children with severe wetting resistant to DESMOPRESSIN

17.2.1.11 Desmopressin treatment after not responding to previous desmopressin treatment for children with severe bedwetting

One observational study **Wikstrom (1996)**¹⁶⁶ considered desmopressin treatment for children who had not responded to 3 sets of treatment including the final treatment being desmopressin. Children were given 20 to 40 µg 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 µg 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 enuresis alarm as well for 12 weeks, those who had not responded were taken off desmopressin and given an enuresis alarm instead for 12 weeks. In some children who failed treatment was stopped for 6 to 9 months and then started again.

Children with monosymptomatic nocturnal enuresis not responding to alarm therapy

17.2.1.1 Alarm and desmopressin for children with monosymptomatic nocturnal enuresis for children who have not responded to alarm therapy

One observational study, **Vogt (2009)**¹⁵⁹ considered alarms combined with desmopressin for children who do not respond to 3 months of alarm treatment. The study outcomes were the number of children who became dry (defined as a maximum of 2 wet nights per month) and the number of children who relapsed after 1 year. Children had a mean age of 10.05 years and had 3 months of treatment. The study showed 11 out of 14 children became dry and after 1 year no children had relapsed when treated with alarm and desmopressin.

Children with monosymptomatic nocturnal enuresis not responding to desmopressin therapy

17.2.1.1 Desmopressin and placebo compared to desmopressin and tolterodine placebo for children with monosymptomatic nocturnal enuresis for children who have not responded to desmopressin therapy

One randomised controlled trial **Austin (2008)**³ compared 600 micrograms desmopressin and placebo to 600 micrograms desmopressin and 4 mg tolterodine for children who have not responded to desmopressin.

Table 17-11: Desmopressin and placebo compared to desmopressin and tolterodine for monosymptomatic children who have not responded to desmopressin - Clinical summary of findings

Outcome	Desmopressin and placebo	Desmopressin and tolterodine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	1/16 (6.3%)	3/18 (16.7%)	RR 0.38 (0.04 to 3.25)	104 fewer per 1000 (from 160 fewer to 376 more)	LOW
Number of children who achieved 50% improvement	4/16 (25%)	5/18 (27.8%)	RR 0.9 (0.29 to 2.78)	28 fewer per 1000 (from 197 fewer to 495 more)	LOW

17.2.1.2 Enuresis alarm treatment after not responding to desmopressin treatment children with monosymptomatic nocturnal enuresis

One observational study **Tuygun (2007)**¹⁵¹ compared desmopressin (20 to 40 micrograms intranasal desmopressin or 200 micrograms to 400 micrograms tablet desmopressin) to enuresis alarms, in the second part of the trial those who had failed to respond to desmopressin were entered into a third treatment group of enuresis alarm. The study outcomes were the number of children who achieved a greater than 90% reduction in the number of wet nights, the number of children who had a 50 to 90% reduction in the number of wet nights, the mean number of wet nights in the final month of treatment and the number of children who relapsed at 6 months. The median age of children was 8 years and each had 3 months of treatment. In the group of children treated with enuresis alarm after failing desmopressin treatment the trial showed 13 out of 19 (68.42%) achieved a >90% decrease in number of wet nights; 3 out of 19 (15.78%) achieved 50 to 90% reduction in the number of wet nights; at 6 months 6 out of 9 (31.57%) had relapsed; the mean number of wet nights per week at the end of treatment was 5.5 (SD 10.65).

These results can be compared to enuresis alarm therapy as first line treatment; the trial showed in the enuresis alarm as second line treatment group 13 out of 19 (68.42%) achieved a >90% decrease in number of wet nights, this was compared to 20 out of 35 children (57.14%) who had enuresis alarm treatment as first line therapy. 3 out of 19 (15.78%) children in the enuresis alarm as second line treatment group achieved 50 to 90% reduction in the number of wet nights compared to 9 out of 35 (27.71%) children in enuresis alarm treatment as first line therapy group. After 6 months 6 out of 9 (31.57%) of children in the enuresis alarm as second line treatment had relapsed compared to 10 out of 35 children (28.57%) in the enuresis alarm as first line therapy group. None of these differences were significant. In the enuresis alarm as second line treatment the mean number of wet nights per week at the end of treatment was 5.5 (SD 10.65), compared to 23.2 (SD 6.23) in the enuresis alarm as first line treatment. The difference in mean number of wet nights was significant.

17.2.1.1 Desmopressin and alarm for children with monosymptomatic nocturnal enuresis for children who have not responded to desmopressin therapy

One observational study, **Vogt (2009)**¹⁵⁹ considered desmopressin combined with alarm for children who are treatment resistant to 3 months of desmopressin treatment. The study considered children with monosymptomatic nocturnal enuresis. The study outcomes were the number of children who became dry (defined as a maximum of 2 wet nights per month) and the number of children who relapsed after 1 year. Children had a mean age of 10.05 years and had 3 months of

treatment. The study showed 11 out of 14 children became dry and after 1 year no children had relapsed when treated with alarm and desmopressin.

17.2.1.2 Desmopressin and oxybutynin for children with monosymptomatic nocturnal enuresis who are non responders to desmopressin

One observational study, **Radvanska (2006)**¹²⁴ considered desmopressin combined with oxybutynin for children with monosymptomatic nocturnal enuresis. **Radvanska (2006)**¹²⁴ considered children who were non-responders (less than 50% improvement) to a 2 week trial of 20 micrograms intranasal desmopressin. Children had 20 micrograms intranasal desmopressin and 5 mg oxybutynin twice daily.

Side effects of second line treatments

17.2.1.3 Enuresis alarm with desmopressin compared to enuresis alarm with placebo for children treatment resistant to desmopressin

One randomised controlled trial, **Gibb (2004)**⁶³, compared enuresis alarm with desmopressin to enuresis alarm with placebo.

Table 17-12: Enuresis alarm and desmopressin compared to enuresis alarm and placebo- Clinical summary of findings

Outcome	Alarm and desmopressin	Alarm and placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children with headaches	1/101 (1%)	0/106 (0%)	RR 3.15 (0.13 to 76.37)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

17.2.1.4 Desmopressin compared to placebo for children treatment resistant to enuresis alarms with severe bedwetting

One randomised controlled trial, **Stenberg (1994)**¹⁴¹, compared desmopressin to placebo.

Table 17 -13: Desmopressin compared to placebo - Clinical summary of findings

Outcome	Desmopressin	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children with headaches	5/10 (50%)	0/10 (0%)	RR 11 (0.69 to 175.86)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW

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Number of children with abdominal pain	6/10 (60%)	0/10 (0%)	RR 13 (0.83 to 203.83)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Number of children with nausea and vertigo	1/10 (10%)	0/10 (0%)	RR 3 (0.14 to 65.9)	0 more per 1000 (from 0 fewer to 0 more)	LOW

17.2.1.5 Imipramine compared to tolterodine for children treatment resistant to enuresis alarms and desmopressin

One randomised controlled trial, **Neveus (2008)**¹¹³ considered imipramine compared to tolterodine.

Table 17-14: Imipramine compared to tolterodine - Clinical summary of findings

Outcome	Imipramine	Tolterodine	Relative risk (95% CI)	Absolute effect	Quality
Number of children with slight mood change	3/27 (11.1%)	1/27 (3.7%)	RR 3 (0.33 to 27.06)	74 more per 1000 (from 25 fewer to 964 more)	LOW
Number of children with insomnia	2/27 (7.4%)	0/27 (0%)	RR 5 (0.25 to 99.51)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Number of children with palpitations	1/27 (3.7%)	0/27 (0%)	RR 3 (0.13 to 70.53)	0 more per 1000 (from 0 fewer to 0 more)	LOW
Number of children with slight nausea	2/27 (7.4%)	0/27 (0%)	RR 5 (0.25 to 99.51)	0 more per 1000 (from 0 fewer to 0 more)	LOW

17.2.1.6 Tolterodine compared to imipramine for children treatment resistant to enuresis alarms and desmopressin

One randomised controlled trial, **Neveus (2008)**¹¹³ considered tolterodine compared to imipramine.

Table 17-15: Tolterodine compared to imipramine - Clinical summary of findings

Outcome	Tolterodine	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children with slight mood change	1/27 (3.7%)	3/27 (11.1%)	RR 0.33 (0.04 to 3.01)	74 fewer per 1000 (from 107 fewer to 223 more)	LOW

17.2.2 Health economic evidence review

Given the lack of published evidence assessing the cost-effectiveness of different interventions used in the initial and subsequent treatment of bedwetting, the GDG identified this area as high priority for original economic analysis. Therefore, a cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK National Health Service and Personal Social Services perspective. The time horizon for the analysis was 13 years, modelling patients from the time they entered at age 7 years until they reached age 20.

A summary of the analysis is provided below. The full report is presented in appendix G.

Summary of results

The results of the probabilistic sensitivity analysis are summarised in table 17-16 in terms of mean total costs and mean total QALYs and mean net benefit for each treatment sequence, where each mean is the average of 20,000 simulated estimates. The option with the greatest mean net benefit is the most cost-effective at a specified threshold (for example, £20,000). The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

Table 17-16: Basecase probabilistic sensitivity analysis results

Treatment sequence	Mean cost	Mean QALYs	Net Benefit (threshold= £20,000 per QALY)	Probability that strategy is most cost-effective (threshold =£20,000 per QALY)
No Treatment	£0	19.734	£394,684	0.0%
Alarm - Imipramine	£206	19.901	£397,816	0.4%
Imipramine - Desmopressin	£406	19.914	£397,875	0.0%
Imipramine - Desmopressin -	£514	19.922	£397,929	0.0%

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Desmopressin+Anticholinergic				
Desmopressin - Imipramine	£298	19.912	£397,943	0.7%
Imipramine - Alarm - Desmopressin	£374	19.927	£398,169	0.0%
Imipramine - Alarm - Desmopressin - Desmopressin+Anticholinergic	£434	19.932	£398,203	0.0%
Desmopressin - Alarm - Imipramine	£304	19.952	£398,729	0.3%
Alarm - Desmopressin - Imipramine	£275	19.955	£398,814	0.1%
Alarm - Imipramine - Desmopressin	£310	19.959	£398,877	0.0%
Alarm - Imipramine - Desmopressin - Desmopressin+Anticholinergic	£367	19.964	£398,910	0.0%
Desmopressin - Alarm+Desmopressin - Imipramine	£378	19.978	£399,178	3.1%
Desmopressin	£314	19.981	£399,297	7.1%
Alarm - Alarm+Desmopressin - Imipramine	£252	19.981	£399,357	13.1%
Desmopressin - Desmopressin+Anticholinergic	£426	19.990	£399,370	19.8%
Alarm - Desmopressin	£280	19.991	£399,549	4.9%
Desmopressin - Alarm+Desmopressin - Desmopressin	£410	19.998	£399,551	3.3%
Alarm - Desmopressin - Desmopressin+Anticholinergic	£346	19.997	£399,592	5.6%
Desmopressin - Alarm+Desmopressin - Desmopressin / Desmopressin+Anticholinergic	£433	20.002	£399,603	3.9%
Desmopressin - Alarm - Desmopressin	£350	19.998	£399,609	7.7%
Alarm - Alarm+Desmopressin - Desmo	£258	19.995	£399,640	15.9%
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£281	19.996	£399,647	8.3%
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£373	20.001	£399,647	5.8%

The results of the incremental analysis in the probabilistic analysis, excluding dominated and extendedly dominated strategies, are presented in table 17-17.

Table 17-17: Incremental analysis of basecase probabilistic results with dominated and extendedly dominated sequences removed

Treatment sequence	Mean cost (£)	Incremental Cost (£)	Mean QALYs	Incremental QALYs	ICER (£/QALY)
No Treatment	£0		19.73421		
Alarm - Alarm+Desmopressin - Desmo	£258	£258	19.99489	0.26068	£988
Alarm - Alarm+Desmopressin - Desmopressin - Desmopressin+Anticholinergic	£282	£24	19.9964	0.00151	£15,828
Desmopressin - Alarm - Desmopressin / Desmopressin+Anticholinergic	£373	£91	20.00099	0.00459	£19,891
Desmopressin - Alarm+Desmopressin -	£433	£61	20.00183	0.00084	£72,143

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Desmopressin / Desmopressin+Anticholinergic					
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The differences between intervention sequences were relatively small and the probabilistic results indicated substantial uncertainty around the mean cost and benefit estimates. Small changes to the model inputs appears to result in substantial changes to the conclusions about modelled sequences' relative and overall cost-effectiveness.

Results of the basecase probabilistic analysis indicate that a cost-effective second line treatment for children who have not responded to alarm alone is combined alarm and desmopressin. And for children who have not responded to desmopressin alone, a cost-effective second line option is a switch to alarm alone. However, in a group of children for whom alarms are not appropriate, it is cost-effective to try the addition of an anticholinergic to desmopressin. Even as a second line intervention, imipramine was never found to be cost-effective.

The economic analysis conducted and presented here represents the first undertaken to assess the cost-effectiveness of interventions used in the treatment of children with bedwetting. And although the analysis is directly applicable to decision making in the UK NHS, it has some potentially serious limitations, some of which may significantly impact the overall conclusions that can be drawn. The main limitations of the analysis are related to the fact that assumptions had to be made in the absence of evidence. Some of these key assumptions centre around:

- treatment effectiveness being independent of age
- health care resource use having been estimated by GDG
- utility weights having been estimated by GDG

A full discussion of these can be found in appendix G.

17.2.3 Evidence statements

Studies include children with bedwetting and possible daytime symptoms

Children who have not responded to ENURESIS ALARM therapy

Enuresis alarm compared to modified dry bed training with an enuresis alarm

Butler (1988)²⁴, Butler (1990)²⁶

- Two studies showed children treated with an enuresis alarm were more likely to achieve 14 consecutive dry nights compared to children treated with modified dry bed training and an enuresis alarm. Relative risk 1.52, 95% CI 1.14, 2.04. Children in Butler (1988) had a mean age of 9.7 years and had 16

weeks of treatment, 48.6% were resistant to enuresis alarm treatment. In Butler (1990) the mean age was 10.6 years and treatment was for 16 weeks, all children were resistant to enuresis alarms.

- One study showed children treated with modified dry bed training with an enuresis alarm had 0.76 fewer wet nights per week at the end of treatment compared to children treated with an enuresis alarm. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed children treated with an enuresis alarm had 0.2 fewer wet nights per week at the end of treatment compared to children treated with modified dry bed training with an enuresis alarm. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- Children in Butler (1988) had a mean age of 9.7 years and had 16 weeks of treatment, 48.6% were resistant to enuresis alarm treatment. In Butler (1990) the mean age was 10.6 years and treatment was for 16 weeks, all children were resistant to enuresis alarms.
- Two studies showed there was no statistically significant difference in the number of children who relapsed between children treated with an enuresis alarm and children treated with modified dry bed training with an enuresis alarm. Relative risk 1.14, 95% CI 0.63, 2.07. Children in Butler (1988) had a mean age of 9.7 years and had 16 weeks of treatment, 48.6% were resistant to enuresis alarm treatment. In Butler (1990) the mean age was 10.6 years and treatment was for 16 weeks, all children were resistant to enuresis alarms.

Butler (1990) ²⁶

- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with an enuresis alarm and children treated with modified dry bed training and an enuresis alarm. Relative risk 0.5, 95% CI 0.05, 5.15. Children had a mean age was 10.6 years and treatment was for 16 weeks, all children were resistant to enuresis alarms.

Desmopressin compared to placebo

Dimson (1986) ⁴²

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with 20 µg intranasal desmopressin and children treated with a placebo. Relative risk 5, 95% CI 0.26, 97. Children had an age range of 6 to 13 years and had 2 weeks of treatment. All were resistant to enuresis alarm treatment,
- One study showed children treated with 20 µg intranasal desmopressin had 1.6 fewer wet nights per week at the end of treatment than children treated with placebo. Children had an age range of 6 to 13 years and had 2 weeks of treatment, all were resistant to enuresis alarm treatment. The studies did not give standard deviation values and therefore the mean difference and CI were not estimable.
- One study showed all children treated with 20 µg intranasal desmopressin (2 out of 2) relapsed. No children in the placebo group became dry and therefore could not relapse. Children had an age range of 6 to 13 years and had 2 weeks of treatment. All were resistant to enuresis alarm treatment.

Children who have not responded to DESMOPRESSIN

Enuresis alarm and placebo compared to enuresis alarm and desmopressin

Gibb (2004) ⁶³

- One study showed there was no statistically significant difference in the number of children who achieved 28 consecutive dry nights between children treated with an enuresis alarm and placebo and children treated with an enuresis alarm and 20 - 40 µg intranasal desmopressin. Relative risk 0.93, 95% CI 0.71, 1.23. Children had a mean age of 8.3 and 8.5 years and had 2 months of treatment, all children were resistant to desmopressin.
- One study showed children treated with an enuresis alarm and 20 - 40 µg intranasal desmopressin had fewer wet nights per week at the end of treatment compared to children treated with enuresis alarm and placebo. Mean difference 0.6, 95% CI 0.23, 0.97. Children had a mean age of 8.3 and 8.5 years and had 2 months of treatment, all children were resistant to desmopressin.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with an enuresis alarm and placebo and children treated with an enuresis alarm and 20 - 40 µg intranasal desmopressin. Relative Risk 1.8, 95% CI 0.84, 3.85.

Children had a mean age of 8.3 and 8.5 years and had 2 months of treatment, all children were resistant to desmopressin.

Children who have not responded to DESMOPRESSIN / IMIPRAMINE / OXYBUTYNIN

Acupuncture

Serel (2001)¹³⁷

- One study showed children who had previously not responded to treatment with desmopressin, imipramine or oxybutynin could respond to treatment with acupuncture. The study showed 86% of children treated with acupuncture were completely dry within 6 months of starting treatment. Children had a mean age of 10.3 years and had 6 months of treatment. All children had failed to respond to desmopressin, imipramine or oxybutynin.

Studies include children with severe bedwetting and possible daytime symptoms

Children who have not responded to ENURESIS ALARM therapy

Desmopressin compared to placebo for children with severe wetting (excludes studies which only included children with bedwetting) for children who have not responded to enuresis alarm therapy

Terho (1991) ¹⁴⁷

- One study showed children treated with 20 to 40 µg intranasal desmopressin had 2.3 fewer wet nights per week at the end of treatment than children treated with placebo. Children had an age range of 5 to 13 years and had 3 weeks of treatment, 48% were resistant to enuresis alarms. The studies did not give standard deviation values and therefore the mean difference and CI were not estimable.

Studies include children with bedwetting only

Children who have not responded to ENURESIS ALARM therapy or DESMOPRESSIN

Desmopressin compared to placebo

Fjellestad (1987) ⁵⁸

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with 200 µg tablet desmopressin and children treated with placebo. Relative risk 5, 95% CI 0.25, 99.95. Children had a mean age of 9.8 years and had 2 weeks of treatment. 60% were resistant to enuresis alarms and 23% were resistant to desmopressin.
- One study showed children treated with 200 µg tablet desmopressin had 1.5 fewer wet nights per week at the end of treatment compared to children treated with placebo. Children had a mean age of 9.8 years and had 2 weeks of treatment. 60% were resistant to enuresis alarms and 23% were resistant to desmopressin. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.
- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with 20 µg intranasal desmopressin and children treated with placebo. Relative risk 3, 95% CI 0.13, 70.83. Children had a mean age of 9.8 years and had 2 weeks of treatment. 60% were resistant to enuresis alarms and 23% were resistant to desmopressin.

- One study showed children treated with 20 µg intranasal desmopressin had 1.6 fewer wet nights per week at the end of treatment compared to children treated with placebo. Children had a mean age of 9.8 years and had 2 weeks of treatment. 60% were resistant to enuresis alarms and 23% were resistant to desmopressin. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Stenberg (1994) ¹⁴¹

- One study showed children treated with 200 to 400 µg tablet desmopressin had fewer wet nights per week at the end of treatment compared to children treated with placebo. Mean difference -2.3, 95% CI -3.37, -1.03. Children had a mean age of 13.5 years and had 2 weeks of treatment. All were resistant to desmopressin or enuresis alarms.

Tablet desmopressin compared to intranasal desmopressin

Fjellestad (1987) ⁵⁸

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with 20 µg intranasal desmopressin and children treated with 200 µg tablet desmopressin. Relative risk 2, 95% CI 0.19, 20.9. Children had a mean age of 9.8 years and had 2 weeks of treatment. 60% were resistant to enuresis alarms and 23% were resistant to desmopressin.
- One study showed children treated with 20 µg intranasal desmopressin had 0.1 fewer wet nights per week at the end of treatment compared to children treated with 200 µg tablet desmopressin. Children had a mean age of 9.8 years and had 2 weeks of treatment. 60% were resistant to enuresis alarms and 23% were resistant to desmopressin. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable.

Children not respond to ENURESIS ALARM therapy and DESMOPRESSIN

Imipramine compared to placebo

Neveus (2008) ¹¹³

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with 25 to 50 mg imipramine and children treated with placebo. Relative risk 11, 95% CI 0.64, 188.95. Children had a mean age of 9.4 years

and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.

- One study 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 25 to 50 mg imipramine and children treated with placebo. Relative risk 5, 95% CI 0.25, 99.16. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.
- One study showed children treated with 25 to 50 mg imipramine had fewer wet nights in the last 2 weeks of treatment compared to children treated with placebo. Mean difference -3.2, 95% CI -5.72, -0.68. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.
- One study showed there was no difference in the number of children who dropped out between children treated with 25 to 50 mg imipramine and children treated with placebo. Relative risk 1, 95% CI 0.07, 15.12. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.

Imipramine compared to tolterodine

Neveus (2008) ¹¹³

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with 25 to 50 mg imipramine and children treated with 1 to 2 mg tolterodine. Relative risk 11, 95% CI 0.64, 188.95. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.
- One study 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 25 to 50 mg imipramine and children treated with 1 to 2 mg tolterodine. Relative risk 2, 95% CI 0.19, 20.67. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.
- One study showed children treated with 25 to 50 mg imipramine had fewer wet nights in the last 2 weeks of treatment compared to children treated with 1 to 2 mg tolterodine. Mean difference -2.6, 95% CI -5.12, -0.08. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.

- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with 25 to 50 mg imipramine and children treated with 1 to 2 mg tolterodine. Relative risk 3, 95% CI 0.13, 70.3. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.

Tolterodine compared to placebo

Neveus (2008) ¹¹³

- One study showed there was no difference in the number of children who achieved 14 consecutive dry nights between children treated with 1 to 2 mg tolterodine and children treated with placebo. No children in either treatment group achieved 14 consecutive dry nights. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.
- One study 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 1 to 2 mg tolterodine and children treated with placebo. Relative risk 3, 95% CI 0.13, 70.3. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.
- One study showed there was no statistically significant difference in the number of wet nights in the last 2 weeks of treatment between children treated with 1 to 2 mg tolterodine and children treated with placebo. Mean difference -0.6, 95% CI -2.76, 1.56. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with 1 to 2 mg tolterodine and children treated with placebo. Relative risk 0.33, 95% CI 0.01, 7.81. Children had a mean age of 9.4 years and had 5 weeks of treatment. All children were resistant to 6 months of enuresis alarms and desmopressin.

Studies include children with severe bedwetting only

Children who have not responded to DESMOPRESSIN

Desmopressin for children who had previously failed treatment with desmopressin (children with severe bedwetting)

Wikstrom (1997) ¹⁶⁶

- One observational trial showed children who had failed to respond to desmopressin could respond to repeated 20 to 40 µg intranasal desmopressin treatment (50% response rate). Children had an age range of 7 to 18 years and had 6 to 9 months of treatment.
- One observational trial showed children who had failed to respond to repeated treatments with desmopressin could respond to treatment with an enuresis alarm and 20 to 40 µg intranasal desmopressin (53% response rate). Children had an age range of 7 to 18 years and had 6 to 9 months of treatment.

Studies include children with monosymptomatic nocturnal enuresis

Children who have not responded to Alarms

Alarm combined with desmopressin

Vogt (2009) ¹⁵⁹

- One study showed children who had failed to respond to alarms could respond to combined desmopressin and alarm therapy. 11 out of 14 children became dry (maximum of 2 wet nights per month). Children had a mean age of 10.05 years and had 3 months of treatment.
- One study showed children who had failed to respond to alarms could respond to combined desmopressin and alarm therapy, 0 out of 11 children relapsed after 1 year of becoming dry Children had a mean age of 10.05 years and had 3 months of treatment.

Children who have not responded to DESMOPRESSIN

Desmopressin and placebo compared to desmopressin and tolterodine

Austin (2008) ³

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with 600 micrograms desmopressin and placebo and children treated with 600 micrograms desmopressin and 4 mg tolterodine. Relative risk 0.38,

95% CI 0.04, 3.25. Children had a mean age of 10.5 years and had 1 month of treatment. All children were non- or partial responders to desmopressin.

- One study 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 0.6 mg desmopressin and placebo and children treated with 600 micrograms desmopressin and 4 mg tolterodine. Relative risk 0.9, 95% CI 0.29, 2.78. Children had a mean age of 10.5 years and had 1 month of treatment. All children were non- or partial responders to desmopressin.

Enuresis alarm

Tuygun (2007)¹⁵¹

- One study showed children who had failed to respond to desmopressin could respond to second line enuresis alarm therapy; 68.42% achieved a >90% decrease in number of wet nights. Children had a median age of 8 years and had 3 months of treatment.
- One study showed children who had failed to respond to desmopressin could respond to second line enuresis alarm therapy; 15.78% achieved 50 to 90% reduction in the number of wet nights. Children had a median age of 8 years and had 3 months of treatment.
- One study showed children who had failed to respond to desmopressin had a mean number of wet nights per month at the end of treatment was 5.5 (sd 10.65). Children had a median age of 8 years and had 3 months of treatment.
- One study showed children who had failed to respond to desmopressin had a relapse rate of 31.57% at 6 months. Children had a median age of 8 years and had 3 months of treatment.

Desmopressin combined with alarms

Vogt (2009)¹⁵⁹

- One study showed children who had failed to respond to desmopressin could respond to combined desmopressin and alarm therapy. 11 out of 16 children became dry (maximum of 2 wet nights per month). Children had a mean age of 9.81 years and had 3 months of treatment.
- One study showed children who had failed to respond to desmopressin could respond to combined desmopressin and alarm therapy, however 1 out of 11

children relapsed after 1 year of becoming dry Children had a mean age of 9.81 years and had 3 months of treatment.

Desmopressin combined with oxybutynin

Radvanska (2006)¹²⁴

- One observational study showed children treated with desmopressin and oxybutynin significantly reduces the mean number of wet nights per week in children with monosymptomatic nocturnal enuresis who are non responders to desmopressin. Children had a mean age of 10.1 (sd 2.1) years and had 2 weeks of treatment.

Side effects of second line treatments

Desmopressin and enuresis alarm compared to enuresis alarm and placebo for children treatment resistant to desmopressin

Gibb (2004)⁶³

One study showed no statistically significant difference in the number of children having headaches between children treated with enuresis alarms and desmopressin and children treated with enuresis alarm and placebo. Relative risk 3.15, 95% CI 0.13, 76.37. Children had a mean age of 8.3 to 8.5 years and had 2 months of treatment.

Desmopressin compared to placebo for children treatment resistant to enuresis alarms with severe bedwetting

Stenberg (1994)¹⁴¹

- One study showed no statistically significant difference in the number of children having headaches between children treated with desmopressin and children treated with placebo. Relative risk 11, 95% CI 0.69, 175.86. Children had a mean age of 13.5 years and had 2 weeks of treatment.
- One study showed no statistically significant difference in the number of children having abdominal pain between children treated with desmopressin and children treated with placebo. Relative risk 13, 95% CI 0.83, 203.83. Children had a mean age of 13.5 years and had 2 weeks of treatment.
- One study showed no statistically significant difference in the number of children having nausea and vertigo between children treated with desmopressin and children treated with placebo. Relative risk 3, 95% CI 0.14, 65.9. Children had a mean age of 13.5 years and had 2 weeks of treatment.

Imipramine compared to tolterodine for children treatment resistant to enuresis alarms and desmopressin

Neveus (2008)¹¹³

- One randomised controlled trial showed there was no statistically significant difference in the number of children with slight mood change between children treated with imipramine and children treated with tolterodine. Relative risk 3, 95% CI 0.33, 27.06. Children had a mean age of 9.4 years and had 6 weeks of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with insomnia between children treated with imipramine and children treated with tolterodine. Relative risk 5, 95% CI 0.25, 99.51. Children had a mean age of 9.4 years and had 6 weeks of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with palpitations between children treated with imipramine and children treated with tolterodine. Relative risk 3, 95% CI 0.13, 70.53. Children had a mean age of 9.4 years and had 6 weeks of treatment.
- One randomised controlled trial showed there was no statistically significant difference in the number of children with slight nausea between children treated with imipramine and children treated with tolterodine. Relative risk 5, 95% CI 0.25, 99.51. Children had a mean age of 9.4 years and had 6 weeks of treatment.

Tolterodine compared to imipramine for children treatment resistant to enuresis alarms and desmopressin

Neveus (2008)¹¹³

- One randomised controlled trial showed there was no statistically significant difference in the number of children with slight mood change between children treated with tolterodine and children treated with imipramine. Relative risk 0.33, 95% CI 0.04, 3.01. Children had a mean age of 9.4 years and had 6 weeks of treatment.

17.2.4 Health economic evidence statements

NCGC economic evaluation (see appendix G)

- Switching to treatment with combined alarm and desmopressin following a non- or partial response to initial treatment with alarm alone is cost-effective in the treatment of children with bedwetting. This evidence has potentially serious limitations and direct applicability.
- Switching to desmopressin treatment following a non- or partial response to second line treatment with combined alarm and desmopressin is cost-effective in the treatment of children with bedwetting. This evidence has potentially serious limitations and direct applicability.
- The addition of an anticholinergic to desmopressin when desmopressin alone has only produced a partial response is likely to be cost-effective in the treatment of children with bedwetting. This evidence has potentially serious limitations and direct applicability.
- Switching to alarm treatment following a non- or partial response to initial treatment with desmopressin may be a cost-effective step in the treatment of children with bedwetting. This evidence has potentially serious limitations and direct applicability.
- Switching to treatment with combined alarm and desmopressin following a non- or partial response to initial treatment with desmopressin alone is not cost-effective in the treatment of children with bedwetting. This evidence has potentially serious limitations and direct applicability.
- Use of repeated courses of desmopressin in children who experience a recurrence of bedwetting whenever it is withdrawn is cost-effective as a long term management of bedwetting. This evidence has potentially serious limitations and direct applicability.
- Use of repeated courses of combined desmopressin and anticholinergic in children who experience a recurrence of bedwetting whenever treatment is withdrawn is likely to be cost-effective as a long term management of bedwetting. This evidence has potentially serious limitations and direct applicability.

17.2.5 Evidence to recommendations

Relative values of different outcomes

In the evidence review of direct combination the outcomes indicating success of treatment and follow up were examined. The GDG considered that mean reduction in wet nights might be a useful outcome from clinical perspective. The GDG considered that although sustained dryness is what both children and parents or carers wish for when engaging in treatment, when children do not respond to initial treatments, reduction in wet nights may indicate a useful improvement in symptoms even if dryness is not achieved.

Trade off between clinical benefit and harms

The harms related to individual pharmacological choices are outline in the relevant chapters.

Economic considerations

Original modelling undertaken for this guideline showed that the combination of alarm and desmopressin was a likely cost-effective option following a non- or partial response to alarm alone. The addition of desmopressin represents an increase in cost, but one that is reasonable given the associated health gain. The analysis also indicates that if these patients do not achieve a full or sustained response, offering desmopressin alone is a cost-effective next step.

Original modelling undertaken for this guideline showed that when treatment with desmopressin does not produce a response, offering alarm alone may be a cost-effective next step. Clinical evidence indicated that combined alarm and desmopressin treatment following a non-response to desmopressin alone is unlikely to be any more effective than switching to alarm alone. Because combined treatment is more expensive than alarm treatment on its own and no more effective, it would not represent a good use of NHS resources.

Original modelling undertaken for this guideline showed that offering combined anticholinergic with desmopressin where desmopressin alone has produced only a partial response is likely to provide additional health gain and for a reasonable cost to the NHS.

The analysis from which these conclusions are derived showed that there was considerable uncertainty about which sequence of interventions was the most cost-effective, and this was likely caused by the uncertainty around estimates of treatment effectiveness observed in the pair-wise and network meta-analyses.

Quality of evidence (this includes clinical and economic)

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The quality of evidence for outcomes in direct combinations was low or very low.

Other considerations

The GDG used evidence from direct comparisons and health economic analyses to develop the recommendations. The findings of the health economic analysis were important in considering the sequencing of treatments to use following non-response or partial response to initial treatment.

The experience of the GDG was that although alarm and desmopressin in combination following alarm treatment were shown to be clinically and cost effective, some children and parents or carers will not be willing to continue alarm unless they have experienced some benefit from it and may prefer desmopressin alone as the next management option.

The GDG considered that where possible alarm is the first line treatment of choice. When children do not respond to desmopressin considering again whether alarm is a suitable treatment might be appropriate. The child may be older than when they had tried desmopressin or alarm may not have been suitable because of child's age or maturity or for family reasons.

Response rate for alarm in second line treatment is comparable to first line treatment for both full response (90% reduction in the number of wet nights), and partial response (50% reduction in the number of wet nights) and the mean number of wet nights when children were treated with enuresis alarms children following lack of response to desmopressin.

For children who are resistant to desmopressin there is no advantage in continuing desmopressin with an enuresis alarm.

The GDG discussed how the combination of alarm and desmopressin should be used. In the studies of this combination, desmopressin was added in exactly the same way as when using desmopressin on its own, ie. Start with lower dose and then increased dose 1-2 weeks later if no response.

Evidence for the association between certain clinical and/or social or emotional factors and likelihood of response was reviewed as part of the initial assessment chapter, and was regarded as very poor quality. Therefore the recommendation to refer patients who have not responded to repeated courses of treatment for further assessment was informed by the professional opinion of the GDG, based on their clinical knowledge, understanding of pathophysiology of bedwetting and the patient and carer member's personal experiences.

The direct evidence review failed to find benefit for the addition of tolterodine to desmopressin for children who had not responded to desmopressin. The GDG considered the study inadequately powered to show difference and indicated that this combination may be useful in their clinical experience. The health economic analysis supported the clinical consensus of the GDG indicating possible gain at acceptable cost. The GDG however also considered the evidence that the effect of desmopressin and of desmopressin and anti-cholinergic may continue to improve up to 6 months (see Evidence review – **Lee (2005)**⁹⁰). They considered it acceptable to continue treatment for 6 months on desmopressin alone before adding an anti-cholinergic but that the choice between these strategies would need to be individualized to the child and parent or carer.

17.2.6 Recommendations

- 17.2.6.1 *If bedwetting does not respond to initial alarm treatment, offer:*
- *combination treatment with an alarm and desmopressin or*
 - *desmopressin alone if continued use of alarm is no longer acceptable to the child or parents and carers. [1.9.1]*
- 17.2.6.2 *Offer desmopressin alone to children with bedwetting if there has been a partial response to a combination of an alarm and desmopressin following initial treatment with an alarm.[1.9.2]*
- 17.2.6.3 *Consider advising that desmopressin should be taken 1–2 hours before bedtime in children with bedwetting that has either partially responded or not responded to desmopressin taken at bedtime. Ensure that the child can comply with fluid restriction starting from 1 hour before the drug is taken.[1.10.10]*
- 17.2.6.4 *Consider continuing treatment with desmopressin for children with bedwetting that has partially responded, as bedwetting may improve for up to 6 months after starting treatment.[1.10.11]*
- 17.2.6.5 *Consider using repeated courses of desmopressin combined with an anticholinergic in children who have responded to this combination but experience repeated recurrences of bedwetting following previous response to treatment.[1.12.5]*
- 17.2.6.6 *Refer children with bedwetting that has not responded to courses of treatment with an alarm and/or desmopressin for further review and assessment of factors that may be associated with a poor response, such*

as an overactive bladder, an underlying disease or social and emotional factors.[1.11.6]

17.2.6.7 Consider an anticholinergic combined with desmopressin for children who have been assessed by a healthcare professional with expertise in the management of bedwetting that has not responded to an alarm and/or desmopressin and have any of the following:

- bedwetting that has partially responded to desmopressin alone*
 - bedwetting that has not responded to desmopressin alone*
- bedwetting that has not responded to combination of alarm and desmopressin. [1.12.3]*

17.2.6.8 Consider continuing treatment for children with bedwetting that has partially responded to desmopressin combined with an anticholinergic as bedwetting may continue to improve for up to 6 months after starting treatment.[1.12.4]

18 Treatment for children who have recurrence of bedwetting after previous successful treatment for bedwetting

18.1 Introduction

The evidence review searched for studies which considered the clinical and cost effectiveness of treating relapses in children and young people with nocturnal enuresis who had previously been successfully treated. The evidence review did not identify any studies which considered the clinical effectiveness of treating recurrence in children who have previously responded to treatment. The recommendations are informed by the clinical experience of the GDG and the health economic modelling.

18.2 What is the clinical and cost effectiveness of treating relapses in children previously successful in the treatment of children with bedwetting?

18.2.1 Evidence review

No direct evidence was found to inform these recommendations. The network meta-analysis and health economic analysis reported in chapters 24 and appendices F and G.

Two papers describing relapse preventions strategies were found as part of the search for factors predicting outcomes of interventions. Full details of these papers are included in Appendix C. The papers suggested an association between slow withdrawal of desmopressin and lower rates of relapse.

Relapse prevention papers - population studied and tests used:

:

Author	Method	Test Details	Population
Riccabona (1998) ¹²⁸	Reduction in dose of desmopressin	Long term use of desmopressin and reduction in use after successful treatment	NE population

Butler (2001) ³⁰	Alarm and medication	Structured withdrawal from medication or alarms	NE population
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Results from relapse prevention papers:

Author	Setting	Outcome	Prevalence	Impact on treatment
Riccabona (1998) ¹²⁸	Austria	Successful reduction of desmopressin without relapse	Not reported	The study showed rapid increase in dose to achieve dryness followed by 4 to 6 weeks of treatment and then slow reduction in dose lead to fewer relapses
Butler (2001) ³⁰	UK	Successful withdrawal of treatment without causing relapse	Not reported	Patients were offered an alarm on medication free nights. Reducing the medication over 9 to 10 weeks reduced the chance of relapse, the use of an alarm was not related

18.2.2 Health economic evidence review

Given the lack of published evidence assessing the cost-effectiveness of different interventions used in the initial and subsequent treatment of bedwetting, the GDG identified this area as high priority for original economic analysis. Therefore, a cost-utility analysis was undertaken where costs and quality-adjusted life-years (QALYs) were considered from a UK National Health Service and Personal Social Services perspective. The time horizon for the analysis was 13 years, modelling patients from the time they entered at age 7 years until they reached age 20.

A summary of the analysis is provided below. The full report is presented in appendix G.

Assumptions about treatment following a recurrence of bedwetting

The model dealt with patients who responded to treatment but experienced a recurrence of bedwetting following discontinuation of treatment by assuming that they would first resume whatever intervention to which they had most recently responded. Therefore, if they had undergone treatment with alarm and then

experienced a recurrence of bedwetting within 1 week of ending treatment they would immediately resume alarm treatment. If they experienced a recurrence within 3 or 6 months of ending treatment, 45% of patients would resume alarm, 45% would try a new intervention, and 10% would try nothing.

In order to deal with patients who are dry on treatment but regularly experience a recurrence of bedwetting once it is withdrawn, a longer term approach has been modelled for pharmacological interventions used in the third line (and in second line where there is no third line) treatment. Therefore, an additional health state, 'responders on treatment' was created to capture the ongoing maintenance costs of prescriptions and monitoring as well as the differentiated utility weights attached to time spent in this category. The assumption was that most patients will ultimately achieve sustained dryness off treatment, but until then, the objective is to minimise the burden bedwetting imposes on the child and their family.

With regard to the resumption of treatment after a recurrence of bedwetting in this longer term treatment scenario, it was assumed that patients who experience a recurrence immediately (within 1 week following initial success) will face a decreasing likelihood of resuming treatment following each recurrence. After the first recurrence, 100 percent will resume the same treatment. After the second, 95 percent will resume and 5 percent will move on to no treatment (in the natural history model). After the third recurrence, 90 percent resume and 10 percent withdraw and so on until in the end, a maximum of 5 percent resume treatment following each recurrence of bedwetting.

The likelihood of resuming treatment following a recurrence of bedwetting was varied in a sensitivity analysis in order to see how sensitive the results were to the aforementioned assumptions.

Summary of results

Results of the basecase probabilistic analysis concerning first line interventions are presented in the health economic evidence reviews for enuresis alarm (section 12.2.7), desmopressin (section 13.2.7), tricyclic antidepressants (section 15.2.6) and anticholinergics (section 14.2.5). A cost-effective second line treatment for children who have experienced a recurrence following alarm alone is combined alarm and desmopressin. And for children who have experienced a recurrence following desmopressin alone, a cost-effective second line option is a switch to alarm alone. However, in a group of children for whom alarms are not appropriate, it is cost-effective to sustain treatment with desmopressin, taking a one-week break every 3 months. Even as a second line intervention, imipramine was never found to be cost-effective.

In a sensitivity analysis about resumption of treatment following a recurrence of bedwetting, the results of the base case changed. In the base case, it was assumed that 100% of children would resume treatment following a recurrence of bedwetting after 1 week of discontinuing treatment. When this assumption was relaxed and only 50% or 75% of children resumed treatment following a relapse, the cost-effectiveness of alarm – alarm+desmopressin – desmopressin did not change substantially. At 50% resumption the ICER was £1,020 compared to no treatment; at 75%, the ICER was £997 per QALY gained. At 50% resumption, alarm – alarm+desmopressin – desmopressin – desmopressin+anticholinergic was dominated by alarm – alarm+desmopressin – desmopressin. At 75% it had an ICER of £23,100 compared to alarm – alarm+desmopressin – desmopressin. All other treatment sequences were ruled out through dominance or extended dominance in this sensitivity analysis.

The economic analysis conducted and presented here represents the first undertaken to assess the cost-effectiveness of interventions used in the treatment of children with bedwetting. And although the analysis is directly applicable to decision making in the UK NHS, it has some potentially serious limitations, some of which may significantly impact the overall conclusions that can be drawn. The main limitations of the analysis are related to the fact that assumptions had to be made in the absence of evidence. Some of these key assumptions centre around:

- treatment effectiveness being independent of age
- health care resource use having been estimated by GDG
- utility weights having been estimated by GDG

A full discussion of these can be found in appendix G.

18.2.3 Evidence statements

Treatment for children who have relapsed after previous successful treatment for nocturnal enuresis

No studies

No direct clinical evidence was identified which considered the clinical effectiveness of treating children who had relapsed after successful treatment for nocturnal enuresis.

18.2.4 Health economic evidence statements

NCGC economic evaluation (see appendix G)

- Switching to treatment with combined alarm and desmopressin following a recurrence of bedwetting after successful initial treatment with alarm alone is cost-effective in the treatment of children with bedwetting. This evidence has potentially serious limitations and direct applicability.
- Switching to desmopressin treatment following a recurrence of bedwetting after successful second line treatment with combined alarm and desmopressin is cost-effective in the treatment of children with bedwetting. This evidence has potentially serious limitations and direct applicability.
- Switching to alarm treatment following a recurrence of bedwetting after successful initial treatment with desmopressin may be a cost-effective step in the treatment of children with bedwetting. This evidence has potentially serious limitations and direct applicability.
- Switching to treatment with combined alarm and desmopressin following a recurrence of bedwetting following successful initial treatment with desmopressin alone is not cost-effective in the treatment of children with bedwetting. This evidence has potentially serious limitations and direct applicability.

18.2.5 Evidence to recommendations

Relative values of different outcomes

The GDG considered the children and parents or carers starting treatment for bedwetting were seeking an outcome of sustained dryness. A number of different outcomes were used to capture this: the outcome of 14 consecutive dry nights, reduction in wet nights and the mean number of wet nights allow evaluation of the effectiveness of treatment. Follow up rates where available can indicate sustained dryness.

Trade off between clinical benefit and harms

No direct evidence was available but the GDG considered that in general children and families would prefer not to use interventions long term. An alarm requires quite intensive effort by child and family and if a response is not being achieved continued use of an alarm is often unacceptable to children and parents or carers.

Economic considerations

For children who respond fully or partially to desmopressin but then experience a recurrence of wetting when it is withdrawn may benefit from receiving repeated courses of desmopressin. The possible quality of life gains associated with being

consistently dry at night are likely to justify the maintenance cost of ongoing treatment with desmopressin. The cost-effectiveness of this longer term management strategy was explored in the original economic modelling undertaken for this guideline.

Repeated courses of combined desmopressin and anticholinergic are a cost-effective way of sustaining a complete or partial response whilst on treatment for those children who experience a relapse of bedwetting every time they try to stop treatment. The cost-effectiveness of this was explored as part of the original modelling work undertaken for the guideline.

Quality of evidence (this includes clinical and economic)

No direct evidence found

Other considerations

The GDG used evidence from professional experience and health economic analyses to develop the recommendations, as no direct evidence was identified. The findings of the health economic analysis were important in considering the sequencing of treatments to use following use of initial treatment.

The GDG considered that children who were successful on treatment often wished to use that treatment again if treatment had been successful. They recommended that when alarm is used that families should be instructed to use alarm again if bedwetting restarted within 2 weeks without seeking further advice. Desmopressin is less likely to lead to sustained response and for children who had not yet used an alarm the GDG considered that suitability of alarm should be revisited. Otherwise repeated use of desmopressin is supported by health economic analysis.

Licensing requirements are for children to stop desmopressin every three months to evaluate success. The GDG considered that this quite often happens naturally when children forget to take medications. There is some evidence from observational studies that slow withdrawal of desmopressin might reduce relapse and the GDG considered it would not be harmful to do this.

Two types of structured withdrawals were considered in the evidence in the two papers that suggested an association between slow withdrawal of desmopressin and lower rates of relapse: the first Riccabona (1998)¹²⁸ comprised a gradual reduction of dosage by 10 micrograms every four weeks, whilst the second Butler (2001)³⁰ scheduled an increase of “no medication days” phases throughout 8 weeks. The GDG did not consider there was a clear physiological basis for either approach and that evidence was not clear enough to say what method of withdrawal was optimal. They preferred therefore to leave this decision to healthcare professional and family.

Gradual withdrawal of desmopressin is therefore recommended for children who have had recurrences of bedwetting when stop taking desmopressin.

The GDG considered it important that regular medication review be performed for children on recurring doses of any pharmacological agent and wished to include a recommendation to remind healthcare professionals.

18.2.6 Recommendations

- 18.2.6.1 *Consider alarm treatment again if a child who was previously dry with an alarm has started regularly bedwetting again.[1.11.1]*
- 18.2.6.2 *Offer combination treatment with an alarm and desmopressin to children who have more than one recurrence of bedwetting following successful treatment with an alarm.[1.11.2]*
- 18.2.6.3 *Consider using repeated courses of desmopressin in children with bedwetting that has responded to desmopressin treatment but who experience repeated recurrences. Withdraw desmopressin treatment at regular intervals (for 1 week every 3 months) to check if dryness has been achieved when using it for the long-term treatment of bedwetting. [1.11.3]*
- 18.2.6.4 *Gradually withdraw desmopressin rather than suddenly stopping it if a child has had a recurrence of bedwetting following response to previous treatment courses.[1.11.4]*
- 18.2.6.5 *Consider alarm treatment as an alternative to restarting desmopressin for children who have repeated recurrences of bedwetting after successful treatment with desmopressin, if an alarm is now considered appropriate and desirable. [1.11.5]*
- 18.2.6.6 *Perform regular medication reviews for children on repeated courses of drug treatment for bedwetting.[1.1.4]*

19 Psychological treatments for the management of bedwetting

19.1 Introduction

Bedwetting itself may be a source of low self-esteem and bedwetting has been associated with emotional and behavioural disorders. Bedwetting is for example more common in looked-after children. Psychological treatments might be of benefit to the the management of emotional or behavioural problems in their own right but the GDG were interested in whether psychological treatments might be appropriate for some subgroups of children with bedwetting for the management of the bedwetting itself.

Psychotherapy, cognitive therapy, counseling were the interventions included in the evidence review of the effectiveness of psychological interventions.

19.2 What is the clinical and cost effectiveness of psychological interventions for children and young people under 19 years who have bedwetting

19.2.1 Evidence review

19.2.1.1 Psychotherapy compared to enuresis alarm

One randomised controlled trial, **Werry (1965)**¹⁶⁵ compared psychotherapy to enuresis alarms. Psychotherapy was described as 6 to 8 sessions over 3 months.

Table 18-1: Psychotherapy compared to enuresis alarms - Clinical summary of findings

Outcome	Psychotherapy	Alarms	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	2/21 (9.5%)	7/22 (31.8%)	RR 0.3 (0.07 to 1.28)	223 fewer per 1000 (from 296 fewer to 89 more)	VERY LOW

19.2.1.2 3 step program compared to 3 step program and motivational therapy

One randomised controlled trial, **Iester (1991)**⁷⁴ compared a 3 step program to a 3 step program and motivational therapy. The Three Step Program was

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, try 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 3 step program and motivational therapy group had the 3 step program as described and motivational therapy where child, in a group, discussed their problems with a psychiatrist.

Table 18 -2: 3 step program compared to motivational therapy - Clinical summary of findings

Outcome	3 step program	Motivational therapy	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	24/36 (66.7%)	81/96 (84.4%)	RR 0.79 (0.62 to 1.01)	177 fewer per 1000 (from 321 fewer to 8 more)	VERY LOW
Number of children who relapsed at 12 months	2/24 (8.3%)	3/81 (3.7%)	RR 2.25 (0.4 to 12.69)	46 more per 1000 (from 22 fewer to 433 more)	VERY LOW

19.2.1.3 3 step program compared to imipramine

One randomised controlled trial, **Iester (1991)**⁷⁴ compared a 3 step program to imipramine. The Three Step Program was as described above. Children in the imipramine group had 0.9-1.5mg/kg imipramine.

Table 18-3: 3 step program compared to imipramine - Clinical summary of findings

Outcome	3 step program	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	24/36 (66.7%)	14/36 (38.9%)	RR 1.71 (1.07 to 2.74)	276 more per 1000 (from 27 more to 677 more)	VERY LOW
Number of children who relapsed at 12 months	2/24 (8.3%)	2/14 (14.3%)	RR 0.58 (0.09 to 3.69)	60 fewer per 1000 (from 130 fewer to 385 more)	VERY LOW

19.2.1.4 3 step program and motivational therapy compared to imipramine

One randomised controlled trial, **Iester (1991)**⁷⁴ compared a 3 step program and motivational therapy to imipramine. The intervention is described above.

Table 18-4: Motivational therapy and 3 step program compared to imipramine - Clinical summary of findings

Outcome	Motivational therapy	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	81/96 (84.4%)	14/36 (38.9%)	RR 2.17 (1.43 to 3.3)	455 more per 1000 (from 167 more to 895 more)	VERY LOW
Number of children who relapsed at 12 months	3/81 (3.7%)	2/14 (14.3%)	RR 0.26 (0.05 to 1.41)	106 fewer per 1000 (from 136 fewer to 59 more)	VERY LOW

19.2.1.5 Cognitive behaviour therapy compared to no treatment for children with severe wetting

One randomised controlled trial, **Ronen (1992)**¹³¹, compared cognitive behaviour therapy to no treatment. Cognitive behaviour therapy was described as 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”.

Table 18 -5: CBT compared to no treatment - Clinical summary of findings

Outcome	CBT	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who became dry for 3 weeks	15/20 (75%)	0/18 (0%)	RR 28.05 (1.8 to 437.4)	0 more per 1000 (from 0 more to 0 more)	VERY LOW
Mean number of wet nights per 3 weeks at the end of treatment	18	16	-	MD -16.19 (-20.71 to -11.67)	LOW

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Number of children who dropped out	2/20 (10%)	11/18 (61.1%)	RR 0.16 (0.04 to 0.64)	513 fewer per 1000 (from 220 fewer to 587 fewer)	LOW
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19.2.1.6 Cognitive behaviour therapy compared to enuresis alarms for children with severe wetting

One randomised controlled trial, **Ronen (1992)**¹³¹, compared cognitive behaviour therapy to enuresis alarms. Details of intervention are described above.

Table 18-6: CBT compared to enuresis alarms - Clinical summary of findings

Outcome	CBT	Alarms	Relative risk (95% CI)	Absolute effect	Quality
Number of children who became dry for 3 weeks	15/20 (75%)	12/19 (63.2%)	RR 1.19 (0.78 to 1.82)	120 more per 1000 (from 139 fewer to 518 more)	VERY LOW
Mean number of wet nights per 3 weeks at the end of treatment	18	15	-	MD -0.2 (-3.05 to 2.65)	VERY LOW
Number of children failed or relapsed at 6 months	3/18 (16.7%)	9/15 (60%)	RR 0.28 (0.09 to 0.85)	432 fewer per 1000 (from 90 fewer to 546 fewer)	VERY LOW
Number of children who dropped out	2/20 (10%)	4/19 (21.1%)	RR 0.47 (0.1 to 2.3)	112 fewer per 1000 (from 190 fewer to 274 more)	VERY LOW

19.2.1.7 Cognitive behaviour therapy compared to star charts for children with severe wetting

One randomised controlled trial, **Ronen (1992)**¹³¹, compared cognitive behaviour therapy to star charts. Details of CBT are described above; stars were given as a reward for a dry night.

Table 18-7: CBT compared to enuresis star charts - Clinical summary of findings

Outcome	CBT	Star charts	Relative risk (95% CI)	Absolute effect	Quality
Number of children who became dry for 3 weeks	15/20 (75%)	6/20 (30%)	RR 2.5 (1.22 to 5.11)	450 more per 1000 (from 66 more to 1000 more)	VERY LOW
Mean number of wet nights per 3 weeks at the end of treatment	18	14	-	MD -2.3 (-5.5 to 0.9)	VERY LOW
Number of children failed or relapsed at 6 months	3/18 (16.7%)	8/14 (57.1%)	RR 0.29 (0.09 to 0.9)	405 fewer per 1000 (from 57 fewer to 520 fewer)	VERY LOW
Number of children who dropped out	2/20 (10%)	6/20 (30%)	RR 0.33 (0.08 to 1.46)	201 fewer per 1000 (from 276 fewer to 138 more)	VERY LOW

19.2.2 Network Meta-Analysis

Psychological treatments were amongst the interventions included in a network meta-analyses of interventions used for nocturnal enuresis. The summary of results of this analysis is presented in chapter 24 and a detailed description of the analysis is presented in appendix F. If studies did not meet the inclusion criteria of the network meta-analysis protocol as stated in appendix F they were not included in the network meta-analysis

19.2.3 Evidence statements

Studies include children with bedwetting and possible daytime symptoms

Psychotherapy compared to no treatment or enuresis alarms

Werry (1965)¹⁶⁵

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with psychotherapy (6 to 8 sessions over 3 months) and children

treated with enuresis alarms. Relative risk 0.3, 95% CI 0.07, 1.28. Children had a mean age of 9.79 years and had 3 to 4 months of treatment.

- One study showed all children had an improved psychological score when treated for nocturnal enuresis. Children had a mean age of 9.79 years and had 3 to 4 months of treatment.

3 step program compared to no treatment

3 step program and motivational therapy compared to no treatment

3 step program compared to 3 step program and motivational therapy

lester (1991) ⁷⁴

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children treated with a 3 step program and children treated with a 3 step program and motivational therapy. Relative risk 0.79, 95% CI 0.62, 1.01. Children had an age range of 6 to 11 years and had 6 months of treatment.
- One study showed there was no statistically significant difference in the number of children who relapsed at 12 months between children treated with a 3 step program and children treated with a 3 step program and motivational therapy. Relative risk 2.25, 95% CI 0.40, 12.69. Children had an age range of 6 to 11 years and had 6 months of treatment.

3 step program compared to imipramine

lester (1991) ⁷⁴

- One study showed children treated with a 3 step program were more likely to achieved 14 consecutive dry nights compared to children treated with imipramine. Relative risk 1.71, 95% 1.07, 2.74. Children had an age range of 6 to 11 years and had 6 months of treatment.
- One study showed there was no statistically significant difference in the number of children who relapsed at 12 months between children treated with a 3 step program and children treated with imipramine. Relative risk 0.58, 95% CI 0.09, 3.69. Children had an age range of 6 to 11 years and had 6 months of treatment.

3 step program and motivational therapy compared to imipramine

lester (1991) ⁷⁴

- One study showed children treated with a 3 step program and motivational therapy were more likely to achieved 14 consecutive dry nights compared to children treated with imipramine. Relative risk 2.17, 95% 1.43, 3.30. Children had an age range of 6 to 11 years and had 6 months of treatment.
- One study showed there was no statistically significant difference in the number of children who relapsed at 12 months between children treated with a 3 step program and motivational therapy and children treated with imipramine. Relative risk 0.26, 95% CI 0.05, 1.41. Children had an age range of 6 to 11 years and had 6 months of treatment.

Unstructured play therapy compared to no treatment

Studies include children with severe bedwetting

CBT compared to no treatment (for children with severe wetting)

Ronen (1992) ¹³¹

- One study showed children treated with cognitive behaviour therapy were more likely to be dry for 3 consecutive weeks compared to children who had no treatment. Relative risk 28.05, 95% CI 1.80, 437.40. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.
- One study showed children treated with cognitive behaviour therapy had fewer wet nights per 3 weeks compared to children who had no treatment. Mean difference -16.19, -20.71, -11.67. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.
- One study showed children treated with cognitive behaviour therapy were less likely to drop out compared to children who had no treatment. Relative risk 0.16, 95% 0.04, 0.64. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.

CBT compared to enuresis alarm

Ronen (1992) ¹³¹

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- One study showed there was no statistically significant difference in the number of children who achieved dryness for 3 consecutive weeks between children treated with cognitive behaviour therapy and children treated with an enuresis alarm. Relative risk 1.19, 95% CI 0.78, 1.82. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.
- One study showed there was no statistically significant difference in the mean number of wet nights per 3 weeks at the end of treatment between children treated with cognitive behaviour therapy and children treated with an enuresis alarm. Mean difference -0.20, 95% CI -3.05, 2.65. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.
- One study showed children treated with an enuresis alarm were more likely to fail to achieve dryness or relapse at 6 months compared to children treated with cognitive behaviour therapy. Relative risk 0.28, 95% CI 0.09, 0.85. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.
- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with cognitive behaviour therapy and children treated with an enuresis alarm. Relative risk 0.47, 95% CI 0.10, 2.30. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.

CBT compared to star chart

Ronen (1992) ¹³¹

- One study showed children treated with cognitive behaviour therapy were more likely to be dry for 3 consecutive weeks compared to children treated with star charts. Relative risk 2.50, 95% CI 1.22, 5.11. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.
- One study showed there was no statistically significant difference in the mean number of wet nights per 3 weeks at the end of treatment between children treated with cognitive behaviour therapy and children treated with star charts. Mean difference -2.30, 95% CI -5.50, 0.90. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.
- One study showed children treated with star charts were more likely to fail to become dry or relapse at 6 months compared to children treated with cognitive behaviour therapy. Relative risk 0.29, 95% CI 0.09, 0.90. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.

- One study showed there was no statistically significant difference in the number of children who dropped out between children treated with cognitive behaviour therapy and children treated with star charts. Relative risk 0.33, 95% CI 0.08, 1.46. Children in the trial had a mean age of 10.05 years and had treatment for 18 weeks.

NCGC network meta-analysis (see appendix F)

- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with psychotherapy and no treatment / placebo. Relative risk 5.972, 95% CI 1.068, 8.977. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**
- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with a 3 step programme and no treatment / placebo. Relative risk 8.213, 95% CI 4.251, 9.479. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**
- **The NCGC NMA showed there was a statistically significant difference in the number of children who achieved a full response between children treated with a 3 step programme and motivational therapy and no treatment / placebo. Relative risk 9.07, 95% CI 6.555, 9.594. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**
- **The NCGC NMA showed there was no statistically significant difference in the number of children who achieved a full response between children treated with play therapy and no treatment / placebo. Relative risk 0.06796, 95% CI 0.004, 2.407. Children had an age range of 5 to 17 years and treatment for a minimum of 12 weeks.**

For estimates of treatment effect relative to other active comparators, please see section 24.4 in chapter 24.

19.2.4 Evidence to recommendations

Relative values of different outcomes

The GDG considered the children and parents or carers starting treatment for bedwetting were seeking an outcome of sustained dryness. A number of different outcomes were used to capture this: the outcome of 14 consecutive dry nights,

reduction in wet nights and the mean number of wet nights allow evaluation of the effectiveness of treatment. Follow up rates indicate where available can indicate sustained dryness. For children who had not responded to other treatments, reduction in mean wet nights might give an indication of some improvement

Trade off between clinical benefit and harms

No evidence of harms

Economic considerations

Although no economic evidence was identified to assess the cost-effectiveness of psychotherapy as a treatment for bedwetting, the clinical evidence did not support its use as a specific treatment. The poor effectiveness evidence does not justify the substantial cost to the NHS that a programme of psychotherapy in this population would represent. No economic evidence was found to evaluate the cost-effectiveness of cognitive behavioural therapy in a population with severe bedwetting. It is very unlikely that CBT, a costly and intensive intervention, as a first line treatment in this particular population is cost-effective and therefore other interventions should be offered first.

There is no clinical or economic evidence to support consultation with a professional with psychological expertise in children with emotional and/or behavioural problems, but the GDG considered that it could be useful and might represent reasonable cost to the NHS.

Quality of evidence (this includes clinical and economic)

The quality of evidence available was low

Other considerations

The GDG considered that bedwetting can be associated with emotional behavioural problems and the attention to these problems may be the appropriate course of action for some children rather than concentrating on treatments for bedwetting. The GDG considered that these children need any psychological or behavioural treatment as appropriate to their problem.

The available evidence on psychotherapy as treatment did not describe the psychotherapy adequately and no details were given about how it addressed bedwetting. The RCT was in a severe wetting population and the GDG considered insufficient evidence for recommending psychotherapy. They considered it

important that children with bedwetting who also have psychological problems have access to standard treatments which have a better evidence base.

The GDG were interested in the RCT which described use of CBT in a population with severe bedwetting. The components of CBT that were described are consistent with models used in clinical practice. The CBT was quite intensive and the GDG considered it a promising intervention but the study was small and not powered enough to show effect. CBT might be a modality of treatment suitable for some children but the evidence was inadequate to make a broad recommendation. A research recommendation has been made to evaluate the effectiveness of psychological therapies, particularly CBT.

19.2.5 Recommendations

19.2.5.1 Consider involving a professional with psychological expertise for children with bedwetting and emotional or behavioural problems.[1.3.15]

20 Information and Educational interventions for the management of bedwetting

20.1 Introduction

It is an accepted part of modern health care that healthcare professionals should inform patients and where appropriate their families and carers about the health problem being treated and management options. In a condition such as bedwetting where treatments may involve significant effort from child and family, information and explanation are considered extremely important. Information and advice about such aspects as fluid intake may of themselves be adequate treatment for some children. The GDG were interested in whether there were any specific informational or educational interventions which influenced outcomes for children.

The evidence review on the effectiveness of information and educational interventions included the following interventions: advice on the condition and treatments including oral, written, computer based, video, DVD and clinic and home based delivery methods.

20.2 What is the clinical and cost effectiveness of information and educational interventions for children and young people under 19 years who have bedwetting

20.2.1 Evidence review

20.2.1.1 CD rom information and enuresis alarm intervention compared to usual enuresis alarm treatment

Table 20-1: CD rom information and enuresis alarm intervention compared to usual enuresis alarm treatment - Clinical summary of findings

Outcome	CD rom and alarm	Usual alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	51/108 (47.2%)	41/87 (47.1%)	RR 1 (0.74 to 1.35)	0 fewer per 1000 (from 122 fewer to 165 more)	VERY LOW
Number of children who relapsed at 6 months	30/51 (58.8%)	15/41 (36.6%)	RR 1.61 (1.01 to 2.56)	223 more per 1000 (from 4 more to 571 more)	VERY LOW

20.2.1.2 Written leaflet information and enuresis alarm intervention compared to usual enuresis alarm treatment

Table 20- 2: Written leaflet information and enuresis alarm intervention compared to usual enuresis alarm treatment - Clinical summary of findings

Outcome	Written leaflet and alarm	Usual alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	51/108 (47.2%)	36/75 (48%)	RR 0.98 (0.72 to 1.34)	10 fewer per 1000 (from 134 fewer to 163 more)	VERY LOW
Number of children who relapsed at 6 months	30/51 (58.8%)	18/36 (50%)	RR 1.18 (0.79 to 1.75)	90 more per 1000 (from 105 fewer to 375 more)	VERY LOW

20.2.1.3 CD rom information and enuresis alarm intervention compared to written leaflet information and enuresis alarm intervention

Table 20- 3: CD rom information and enuresis alarm intervention compared to written leaflet information and enuresis alarm intervention - Clinical summary of findings

Outcome	CD and alarm	Written leaflet and alarm	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	41/87 (47.1%)	36/75 (48%)	RR 0.98 (0.71 to 1.36)	10 fewer per 1000 (from 139 fewer to 173 more)	VERY LOW
Number of children who relapsed at 6 months	15/41 (36.6%)	18/36 (50%)	RR 0.73 (0.44 to 1.23)	135 fewer per 1000 (from 280 fewer to 115 more)	VERY LOW

20.2.2 Evidence statements

Redsell (2003)¹²⁶

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children who had a CD rom information and enuresis alarm intervention and children who had usual enuresis alarm treatment. Relative risk 0.98, 95% CI 0.72, 1.34.

Children had a mean age of 7.98 years and had 6 months of treatment.

- One study showed there was no statistically significant difference in the number of children who relapsed after 6 months between children who had a CD rom information and enuresis alarm intervention and children who had usual enuresis alarm treatment. Relative risk 1.18, 95% CI 0.79, 1.75. Children had a mean age of 7.98 years and had 6 months of treatment.

Redsell (2003) ¹²⁶

- One study showed there was no statistically significant difference in the number of children who achieved 14 consecutive dry nights between children who had a written leaflet and children who had usual enuresis alarm treatment. Relative risk 0.98, 95% CI 0.71, 1.36. Children had a mean age of 7.98 years and had 6 months of treatment.
- One study showed there was no statistically significant difference in the number of children who relapsed after 6 months between children who had a written leaflet information and enuresis alarm intervention and children who had usual enuresis alarm treatment. Relative risk 0.73, 95% CI 0.44, 1.23. Children had a mean age of 7.98 years and had 6 months of treatment.

Redsell (2003) ¹²⁶

- One study showed there was no difference in the number of children who achieved 14 consecutive dry nights between children who had a CD rom information and enuresis alarm intervention and children who had a written leaflet information and enuresis alarm intervention. Relative risk 1, 95% CI 0.74, 1.35. Children had a mean age of 7.98 years and had 6 months of treatment.
- One study showed children who had a CD rom information and enuresis alarm intervention were more likely to relapse after 6 months compared to children who had a written leaflet information and enuresis alarm intervention. Relative risk 1.61, 95% CI 1.01, 2.56. Children had a mean age of 7.98 years and had 6 months of treatment.

20.2.3 Evidence to recommendations

Relative values of different outcomes

The GDG considered the children and parents or carers starting treatment for bedwetting were seeking an outcome of sustained dryness. A number of different outcomes were used to capture this: the outcome of 14 consecutive dry nights, reduction in wet nights and the mean number of wet nights allow evaluation of the

effectiveness of treatment. Follow up rates where available can indicate sustained dryness. The GDG considered that 'softer' outcomes would also be relevant and but there was no report of child or parent/carer satisfaction or knowledge and understanding of bedwetting.

Trade off between clinical benefit and harms

No evidence of harm was found.

Economic considerations:

No health economic evidence was available.

Quality of evidence (this includes clinical and economic)

The available clinical evidence was poor.

Other considerations

The available RCT had its information content designed around what the professionals considered important. The content of the DVD was not designed following prior exploration with children or families. An adult talked the child through the information. The RCT did not show one type of delivery is better than the other and the GDG considered it likely that children in the control group in the trial were already likely to be receiving high quality information from the health care professionals they saw.

The GDG considered it important that information should be tailored to the child and the format would also required tailoring to the needs of the child and that literacy issues and cultural issues are likely to be important.

The GDG discussed the importance of support for the patient or carer and considered it important that children and families should be informed of support and help that was available, The GDG were aware of information and groups available to support families and these resources can be vital in informing and supporting families.

20.2.4 Recommendations

20.2.4.1 Offer information, tailored to the child's needs, to children being treated for bedwetting and their parents or carers[1.2.1].

20.2.4.2 Offer information and details of support groups to children being treated for bedwetting and their parents or carers. [1.2.2]

21 Alternative treatments for the management of bedwetting

21.1 Introduction

Parents and carers are often reluctant to use pharmacological agents in children. Many children do not respond to alarms and desmopressin and parents and carers are interested in using alternative treatments for the management of bedwetting. The GDG considered it an important topic as parents and carers regularly ask for advice and if useful it may be appropriate to offer these treatments.

The following interventions were included in the evidence review of the effectiveness of alternative treatments: acupuncture, chiropractic treatment, cranial osteopathy, homeopathy, homotoxicological remedies, hypnotherapy and reflexology. A short description of the intervention is included in the evidence review below.

21.2 What is the clinical and cost effectiveness of alternative treatments for children and young people under 19 years who have bedwetting

21.2.1 Evidence review

21.2.1.1 Hypnotherapy compared to imipramine for children with severe wetting

One randomised controlled trial, **Banjerjee (1993)**⁹ compared hypnotherapy to imipramine. Banjerjee (1993)⁹ considered children with severe wetting. 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 and then given suggestions. Children were given two 30 minutes sessions in the first week, then one session in the second week, further sessions varied but were between once a week and once a fortnight; children receiving imipramine had 25 mg each night, the dose was increased each week if there was no response.

Table 21-1: Hypnotherapy compared to imipramine - Clinical summary of findings

Outcome	Hypnotherapy	Imipramine	Relative risk (95% CI)	Absolute effect	Quality
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Number of children who became completely dry or had a reduced number of wet nights	18/25 (72%)	19/25 (76%)	RR 0.95 (0.68 to 1.32)	38 fewer per 1000 (from 243 fewer to 243 more)	VERY LOW
Number of children who relapsed at 6 months	1/18 (5.6%)	13/19 (68.4%)	RR 0.08 (0.01 to 0.56)	629 fewer per 1000 (from 301 fewer to 677 fewer)	LOW

21.2.1.2 *Acupuncture compared to sham acupuncture for children with night time only wetting*

One randomised controlled trial, **Mao (1998)**⁹⁷ compared acupuncture to sham acupuncture. **Mao (1998)**⁹⁷ considered children with night time only wetting. 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.

Table 21-2: Acupuncture compared to sham acupuncture - Clinical summary of findings

Outcome	Acupuncture	Sham acupuncture	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	30/56 (53.6%)	17/55 (30.9%)	RR 1.73 (1.09 to 2.76)	226 more per 1000 (from 28 more to 544 more)	VERY LOW
Number of children who failed to achieve 14 consecutive dry nights or relapsed after treatment	26/56 (46.4%)	38/55 (69.1%)	RR 0.67 (0.48 to 0.94)	228 fewer per 1000 (from 41 fewer to 359 fewer)	VERY LOW

21.2.1.3 Chiropractic treatment compared to no treatment for children with night time only wetting

One randomised controlled trial, **LeBoeuf (1991)**⁸⁹ compared chiropractic treatment to no treatment. **LeBoeuf (1991)**⁸⁹ considered children with night time only wetting. Chiropractic treatment was described as adjustments of the aberrant spinal movement through observation and palpation each visit.

Table 21-3: Chiropractic treatment compared to no treatment - Clinical summary of findings

Outcome	Chiropractic treatment	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of 2 weeks of treatment	100	71	-	not pooled	VERY LOW

21.2.1.4 Chiropractic treatment compared to sham chiropractic treatment for children with night time only wetting

One randomised controlled trial, **Reed (1994)**¹²⁷ compared chiropractic treatment to sham chiropractic treatment. **Reed (1994)**¹²⁷ considered children with night time only wetting. 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.

Table 21-4: Chiropractic treatment compared to sham chiropractic treatment - Clinical summary of findings

Outcome	Chiropractic treatment	Sham chiropractic treatment	Relative risk (95% CI)	Absolute effect	Quality
Number of children who had greater than 50% improvement in the number of dry nights	8/31 (25.8%)	0/15 (0%)	RR 8.5 (0.52 to 138.16)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
Mean number of wet nights per 2 weeks at follow up	31	15	-	MD -3.6 (-5.93 to -1.27)	VERY LOW

21.2.1.5 *Homotoxicological remedies compared to placebo for children with night time only wetting*

One randomised controlled trial, **Ferrara (2008)**⁵⁵ compared homotoxicological remedies to placebo. **Ferrara (2008)**⁵⁵ considered children with night time only wetting. Homotoxicological remedies were described as 20 solidago drops three times a day and one biopax tablet in the evening; children receiving placebo had 20 placebo drops three times a day and one placebo tablet in the evening.

Table 21-5: Homotoxicological remedies compared to placebo - Clinical summary of findings

Outcome	Homotoxicological remedies	Placebo	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	10/50 (20%)	0/51 (0%)	RR 21.41 (1.29 to 355.87)	0 more per 1000 (from 0 more to 0 more)	VERY LOW

21.2.1.6 *Homotoxicological remedies compared to desmopressin for children with night time only wetting*

One randomised controlled trial, **Ferrara (2008)**⁵⁵ compared homotoxicological remedies to desmopressin. **Ferrara (2008)**⁵⁵ considered children with night time only wetting. Homotoxicological remedies was described as above.

Table 21-6: Homotoxicological remedies compared to desmopressin - Clinical summary of findings

Outcome	Homotoxicological remedies	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved 14 consecutive dry nights	10/50 (20%)	26/50 (52%)	RR 0.38 (0.21 to 0.71)	322 fewer per 1000 (from 151 fewer to 411 fewer)	LOW

21.2.1.7 *Hypnotherapy compared to no treatment for children with night time only wetting*

One randomised controlled trial, **Edwards (1985)**⁴⁵ compared types of hypnotherapy to no treatment. **Edwards (1985)**⁴⁵ considered children with night time only wetting. The types of hypnotherapy were described as trance with suggestions (1), trance without suggestions (2) and suggestions without trance (3). Trance with suggestions

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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.

Table 21-7: Trance with suggestions compared to no treatment - Clinical summary of findings

Outcome	Trance with suggestions	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment	12	12	-	not pooled	VERY LOW
Mean number of wet nights per week at follow up	12	12	-	not pooled	VERY LOW

Table 21-8: Suggestions without trance compared to no treatment - Clinical summary of findings

Outcome	Suggestions without trance	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment	12	12	-	not pooled	VERY LOW
Mean number of wet nights per week at follow up	12	12	-	not pooled	VERY LOW

Table 21 - 9: Trance without suggestions compared to no treatment - Clinical summary of findings

Outcome	Trance without suggestions	No treatment	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment	12	12	-	not pooled	VERY LOW

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Mean number of wet nights per week at follow up	12	12	-	not pooled	VERY LOW
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21.2.1.8 Types of hypnotherapy for children with night time only wetting

One randomised controlled trial, **Edwards (1985)**⁴⁵ compared types of hypnotherapy. **Edwards (1985)**⁴⁵ considered children with night time only wetting. The types of hypnotherapy were as described above.

Table 21-10: Trance with suggestions compared to suggestions without trance - Clinical summary of findings

Outcome	Trance with suggestions	Suggestions without trance	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment	12	12	-	not pooled	VERY LOW
Mean number of wet nights per week at follow up	12	12	-	not pooled	VERY LOW

Table 21-11: Trance with suggestions compared to trance without suggestions - Clinical summary of findings

Outcome	Trance with suggestions	Trance without suggestions	Relative risk (95% CI)	Absolute effect	Quality
Mean number of wet nights per week at the end of treatment	12	12	-	not pooled	VERY LOW
Mean number of wet nights per week at follow up	12	12	-	not pooled	VERY LOW

Table 21-12: Suggestions without trance compared to trance without suggestions - Clinical summary of findings

Outcome	Suggestions without trance	Trance without suggestions	Relative risk (95% CI)	Absolute effect	Quality
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Mean number of wet nights per week at the end of treatment	12	12	-	not pooled	VERY LOW
Mean number of wet nights per week at follow up	12	12	-	not pooled	VERY LOW

21.2.1.9 Laser acupuncture compared to desmopressin for children with monosymptomatic nocturnal enuresis

One randomised controlled trial, **Radmayr (2001)**¹²³ compared laser acupuncture to desmopressin. **Radmayr (2001)**¹²³ considered children with monosymptomatic nocturnal enuresis. 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.

Table 21-13: Laser acupuncture compared to desmopressin - Clinical summary of findings

Outcome	Laser acupuncture	Desmopressin	Relative risk (95% CI)	Absolute effect	Quality
Number of children who achieved at greater than 90% improvement in the number of dry nights	13/20 (65%)	15/20 (75%)	RR 0.87 (0.58 to 1.3)	97 fewer per 1000 (from 315 fewer to 225 more)	VERY LOW
Number of children who achieved 50% to 90% improvement in the number of dry nights	2/20 (10%)	2/20 (10%)	RR 1 (0.16 to 6.42)	0 fewer per 1000 (from 84 fewer to 542 more)	VERY LOW

21.2.1.10 Electro-acupuncture for children with monosymptomatic nocturnal enuresis

One observational trial, **Bjorkstrom (2000)**¹⁴ considered electro-acupuncture for children with monosymptomatic nocturnal enuresis. Children had twenty 30 minute

sessions of electro-acupuncture over 8 weeks of treatment. Electro-acupuncture was described as the child was placed in a supine relaxed position, 7 disposable needles were placed at specific points. For the first 3 sessions these were manual stimulated, after this 2 pairs of needles were connected to an electro-stimulator.

21.2.2 Network Meta-Analysis

Homotoxicological remedies were amongst the interventions included in a network meta-analysis of interventions used for nocturnal enuresis. The summary of results of this analysis is presented in chapter 24 and a detailed description of the analysis is presented in appendix F. If studies did not meet the inclusion criteria of the network meta-analysis protocol as stated in appendix F they were not included in the network meta-analysis

21.2.3 Evidence statements

Studies included children with bedwetting and possible daytime symptoms

Hypnotherapy compared to imipramine (children with had severe bedwetting)

Banjerjee (1993)⁹

- One study 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. Relative risk 0.95, 95% CI 0.68, 1.32. Children had an age range of 5 to 16 years and had 3 months of treatment.
- One study showed children treated with imipramine were more likely to relapse at 6 months compared to children treated with hypnotherapy. Relative risk 0.08, 95% CI 0.01, 0.56. Children had an age range of 5 to 16 years and had 3 months of treatment.

Studies include children with bedwetting only

Acupuncture compared to sham acupuncture

Mao (1998)⁹⁷

- One study showed children treated with acupuncture were more likely to achieve 14 consecutive dry nights compared to children treated with sham acupuncture. Relative risk 1.73, 95% CI 1.09, 2.76. Children had an age range of 5 to 15 years, the length of treatment varied depending upon response.
- One study showed children treated with acupuncture were less likely to fail to achieve 14 consecutive dry nights or relapse after treatment compared to children treated with sham acupuncture. Relative risk 0.67, 95% CI 0.48, 0.94.

Children had an age range of 5 to 15 years, the length of treatment varied depending upon response.

Chiropractic treatment compared to no treatment

Leboeuf (1991)⁸⁹

- One study showed children who had no treatment had 0.5 fewer wet nights per week at the end of treatment compared to children who had chiropractic treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 8.3 years and had 2 weeks of treatment.

Chiropractic treatment compared to sham chiropractic treatment

Reed (1994)¹²⁷

- One study showed there was no statistically significant difference in the number of children who achieved a greater than 50% improvement in the number of dry nights between children treated with chiropractic treatment and children treated with sham chiropractic treatment. Relative risk 8.5, 95% CI 0.52, 138.16. Children had an age range of 5 to 13 years and had 10 weeks of treatment.
- One 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. Mean difference -3.6, 95% CI -5.93, -1.27. Children had an age range of 5 to 13 years and had 10 weeks of treatment.

Homotoxicological remedies compared to placebo

Ferrara (2008)⁵⁵

- One study showed children treated with homotoxicological remedies were more likely to achieve 14 consecutive dry nights compared to children treated with placebo. Relative risk 21.41, 95% CI 1.29, 355.87. Children had a mean age of 8.5 years and had 3 months of treatment.

Homotoxicological remedies compared to desmopressin

Ferrara (2008) ⁵⁵

- One study showed children treated with desmopressin were more likely to achieve 14 consecutive dry nights compared to children treated with homotoxicological remedies. Relative risk 0.38, 95% CI 0.21, 0.71. Children had a mean age of 8.5 years and had 3 months of treatment.

Hypnotherapy compared to no treatment

Edwards (1985) ⁴⁵

- One study showed children treated with trance with suggestions had 2.4 fewer wet nights per week at the end of treatment compared to children who had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.
- One study showed children treated with trance with suggestions had 1.5 fewer wet nights per week at follow up compared to children who had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.
- One study showed children treated with trance without suggestions had 2.7 fewer wet nights per week at the end of treatment compared to children who had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.
- One study showed children treated with trance without suggestions had 2.3 fewer wet nights per week at follow up compared to children who had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.
- One study showed children treated with suggestions without trance had 2.4 fewer wet nights per week at the end of treatment compared to children who

had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.

- One study showed children treated with suggestions without trance had 1.8 fewer wet nights per week at follow up compared to children who had no treatment. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.

Types of hypnotherapy

Edwards (1985) ⁴⁵

- One study 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 compared to children treated with suggestions without trance. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.
- One study showed children treated with suggestions without trance had 0.3 fewer wet nights per week at follow up compared to children treated with trance with suggestions. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.
- One study showed children treated with trance without suggestions had 0.3 fewer wet nights per week at the end of treatment compared to children treated with suggestions without trance. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.
- One study showed children treated with trance without suggestions had 0.5 fewer wet nights per week at follow up compared to children treated with suggestions without trance. No information on variability was given in the

study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.

- One study showed children treated with trance without suggestions had 0.3 fewer wet nights per week at the end of treatment compared to children treated with trance with suggestions. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.
- One study showed children treated with trance without suggestions had 0.8 fewer wet nights per week at follow up compared to children treated with trance with suggestions. No information on variability was given in the study, therefore calculation of standard deviation was not possible and the mean difference and CI were not estimable. Children had a mean age of 10.5 years and had 6 weeks of treatment.

Studies include children with monosymptomatic nocturnal enuresis

Laser acupuncture compared to desmopressin

Radmayr (2001) ¹²³

- One study showed there was no statistically significant difference in the number of children who achieved greater than 90% improvement in the number of wet nights between children treated with laser acupuncture and children treated with desmopressin. Relative risk 0.87, 95% CI 0.58, 1.3. Children had a mean age of 8.6 years in the desmopressin group and 8 years in the acupuncture group and had 3 months of treatment.
- One study showed there was no difference in the number of children who achieved 50% to 90% improvement in the number of wet nights between children treated with laser acupuncture and children treated with desmopressin. Relative risk 1, 95% CI 0.16, 6.42. Children had a mean age of 8.6 years in the desmopressin group and 8 years in the acupuncture group and had 3 months of treatment.

Electro-acupuncture

Bjorkstom (2000) ¹⁴

- One observational study showed children treated with electro-acupuncture had an increase in the mean number of dry nights during 8 weeks of treatment. Children had a mean age of 10.3 years and had 8 weeks of treatment.
- One observational study showed children treated with electro-acupuncture had an increase in the mean number of dry nights at 3 and 6 months follow up. Children had a mean age of 10.3 years and had 8 weeks of treatment.
- One observational study showed 8% of children treated with electro-acupuncture achieved 90% reduction in the number of wet nights at the end of treatment. Children had a mean age of 10.3 years and had 8 weeks of treatment.
- One observational study showed 22% of children treated with electro-acupuncture achieved 90% reduction in the number of wet nights at 3 months follow up. Children had a mean age of 10.3 years and had 8 weeks of treatment.
- One observational study showed 22% of children treated with electro-acupuncture achieved 90% reduction in the number of wet nights at 6 months follow up. Children had a mean age of 10.3 years and had 8 weeks of treatment.
- One observational study showed 26% of children treated with electro-acupuncture achieved 50% to 90% reduction in the number of wet nights at 6 months follow up. Children had a mean age of 10.3 years and had 8 weeks of treatment.

NCGC network meta-analysis (see appendix F)

- **The NCGC NMA showed there was no statistically significant difference in the number of children who achieved a full response between children treated with homotoxicological remedy and no treatment / placebo. Relative risk 4.969, 95% CI 0.820, 9.032. Children had an age range of 5 to 17 years and treatment for a minimum of 8 weeks.**

For estimates of treatment effect relative to other active comparators, please see section 24.4 in chapter 24.

21.2.4 Evidence to recommendations

Relative values of different outcomes

The GDG considered the children and parents or carers starting treatment for bedwetting were seeking an outcome of sustained dryness. A number of different outcomes were used to capture this: the outcome of 14 consecutive dry nights, reduction in wet nights and the mean number of wet nights allow evaluation of the effectiveness of treatment. Follow up rates where available can indicate sustained dryness.

Trade off between clinical benefit and harms

No evidence of harm was found.

Economic considerations:

No health economic evidence was available and the clinical evidence was insufficient to make a recommendation for acupuncture, hypnotherapy and chiropractic. It is highly uncertain as to whether these interventions would represent good value for money.

Quality of evidence (this includes clinical and economic)

The available clinical evidence was poor.

Other considerations

Accupuncture: Three studies each considering different types of acupuncture, with a range of results. All studies appeared to show some improvement with the result from laser acupuncture the clearest. In this study there appeared some equivalence between the effect of laser acupuncture and desmopressin which is a recognized treatment with a larger evidence base for its use.

The GDG considered that the evidence suggested that acupuncture might be of some benefit. There was an insufficient evidence to recommend acupuncture but the GDG considered it an important research recommendation for acupuncture to be evaluated further.

Hypnotherapy: One small study compared hypnotherapy to imipramine and children treated with hypnotherapy were less likely to relapse. The GDG considered that hypnotherapy may work in similar ways to CBT treatment in that the child learns more about their problem and may be likely to engage more fully with the behavioral components of management.

The GDG made a research recommendation for further research on hypnotherapy as a treatment for bedwetting.

Chiropractic: The evidence review found no evidence for effectiveness of chiropractic treatment in bedwetting. One relatively large study comparing chiropractic treatment to no treatment reported that children who had no treatment had 0.5 fewer wet nights per week but did report any statistical information. Study reported adverse effects (2%)

Homotoxicological remedies: A single well conducted study showed homotoxicological remedies are significantly more effective than placebo but significantly less effective than desmopressin. Confidence interval was quite wide and the GDG considered that the outcomes in the placebo arm were poorer than expected. It is unclear what the intervention is, why the ingredients were used and the GDG did not consider the evidence adequate to recommend use or to recommend research in this area.

21.2.5 Recommendations

No recommendations were made

22 Under 5 year olds and management of bedwetting

22.1 Introduction

Definitions of nocturnal enuresis have traditionally used 5 years as a cut off point. From a developmental perspective children are expected to be dry at night at 5 years of age. Epidemiological evidence does indicate that the prevalence of infrequent bedwetting (bedwetting 1-2 nights per week) does fall sharply between the ages of 4 and 6 years of age. During the scoping phase of the guideline it was suggested that the guideline not define a lower age limit in order that the GDG consider whether what advice and treatment is appropriate to younger children in particular whether any factors might reduce the later prevalence of bedwetting. Young children were included as a subgroup in the interevention studies and cohort studies were examined for epidemiological information relevant to the under 5 age group. A co-opted health visitor also attended a GDG meeting to inform the GDG.

22.2 *In children under 5 years old with nocturnal enuresis, are there any preventative, prediction or treatment options which should be considered?*

22.2.1 Evidence review

22.2.1.1 *Epidemiology of bedwetting in children aged under 5 years old*

Three studies which considered the prevalence of bedwetting in children aged under 5 years old, were identified.

Butler (2008)²⁸ conducted an observational study of the prevalence of bedwetting in 13,973 children between the ages of 54 and 115 months (4 ½ and 9 ½ years) in the Avon area of England, UK. The study showed at 54 months (4 ½ years) 8.3% of children had nocturnal enuresis (at least 2 wet nights per week); 21.3% had infrequent bedwetting (less than 2 wet nights per week) and 70.4% had no bedwetting.

Weir (1982)¹⁶⁴ conducted an observational study of the prevalence of night and day wetting in 3 year olds living in Richman borough, London. The results were divided between “non-immigrant” and “immigrant” families. “Immigrant” was described as the mother having lived in the UK or Eire for less than 20 years. The study included 825 children. The study included 342 boys and 364 girls from “non-immigrant” families. For night time wetting the study showed 45.3% of boys and 30.5% of girls

were wet more than twice a week; 10.2% of boys and 9.9% of girls were wet 1 or 2 nights per week; 7.6% of boys and 6.0% of girls were wet less than once a week and 36.8% of boys and 53.6% of girls were never wet at night. The study included 52 boys and 67 girls from “immigrant” families. For night time wetting the study showed 28.8% of boys and 26.9% of girls were wet more than twice a week; 13.4% of boys and 7.5% of girls were wet 1 or 2 nights per week; 1.9% of boys and 7.5% of girls were wet less than once a week and 55.8% of boys and 58.2% of girls were never wet at night.

Kawauchi (2001)⁸⁰ conducted an observational study of the prevalence of bedwetting in a group of children at 3 years old and a follow-up of those at the age of 5 attending a public health clinic in Japan. The study included 157 children, 72 boys and 85 girls. The study showed that the prevalence of bedwetting at 3 years old was 53%. Twenty-four percent of children who had bedwetting were wet 1 to 3 times per month; 22% of children who had bedwetting were wet 1 to 3 times per week; 12% of children who had bedwetting were wet 4 to 6 times per week; and 42% of children who had bedwetting were wet every night. The study showed that the prevalence of bedwetting at 5 years old was 21%. Thirty-three percent of children who had bedwetting were wet 1 to 3 times per month; 27% of children who had bedwetting were wet 1 to 3 times per week; 13% of children who had bedwetting were wet 4 to 6 times per week; and 27% of children who had bedwetting were wet every night.

22.2.2 Evidence statements

Butler (2008)²⁸

- One observational study of 13,973 children conducted in the UK, showed that at 4 ½ years 8.3% of children had nocturnal enuresis; 21.3% had infrequent bedwetting and 70.4% had no bedwetting.

Weir (1982)¹⁶⁴

- One observational study of 825 children conducted in London showed that at 3 years of age, 37.7% of “non-immigrant” children had more than 2 wet nights per week; 10% had 1 to 2 wet nights per week; 6.8% had less than one wet nights per week; and 45.5% were never wet. The study showed that 28% of “immigrant” children had more than 2 wet nights per week; 10% had 1 to 2 wet nights per week; 5% had less than one wet nights per week and 57% were never wet.

Kawauchi (2001)⁸⁰

- One observational study of 157 children in Japan showed 53% of 3 year olds had bedwetting compared to 21% of 5 year olds.

22.2.3 Evidence to recommendations

Relative values of different outcomes

The GDG considered it important not to exclude younger children from appropriate advice.

Trade off between clinical benefit and harms

Bedwetting in children under 5 is common and improves spontaneously in most cases. Available treatments are either not licensed or not suitable for children under 5 years. The GDG considered that advice may be helpful and should not be withheld on basis of age alone.

Economic considerations

Cost-effectiveness modeling undertaken for the guideline indicates that from the perspective of the NHS, treating children with bedwetting is cost-effective compared to not treating. This conclusion applies to children commencing appropriate treatment at ages as young as 5 years. The GDG recognise that a recommendation to treat younger children, where appropriate, is likely to represent a considerable cost impact to the NHS, but they felt that this group could benefit from advice about fluids and toileting and potentially medical treatment.

Quality of evidence (this includes clinical and economic)

No randomized control trials were found assessing management in children under 5 years. The GDG examined cohort studies and epidemiological data to inform their recommendations.

Other considerations

The GDG used professional opinion to inform these recommendations. An invited health visitor also attended a GDG meeting so that the GDG were aware of current health visitor practices in this area.

The GDG considered two issues – how to advise parents or carers about bedwetting in children under 5 and what advice could be offered to reduce the later prevalence of bedwetting.

The GDG considered it important to reassure parents or carers that infrequent bedwetting is common and likely to resolve. The GDG considered that information about how common bedwetting is in this age group would be useful information to give to families. The GDG considered that an assessment of fluid intake, toileting

behaviour and consideration of co-morbidities was important at younger ages. Simple measures such as ensuring adequate fluid intake can improve children's symptoms.

The experience of the GDG was that some children who are continuing to wet the bed at 5 years have not been toilet trained during the day. Parents and carers also use nappies or pull-ups at night and so children do not learn to either hold on or to react to feeling bladder fullness.

Children who have been toilet trained and carry out the appropriate toileting behaviours such as going to toilet, sitting appropriately and are not able to stay dry and clean may have underlying problem that needs further assessment.

22.2.4 Recommendations

22.2.4.1 Reassure parents or carers that many children under 5 years wet the bed, for example, approximately one in five children of 4 and a half years wets the bed at least once a week. [1.15.1]

22.2.4.2 Ask whether toilet training has been attempted, and if not, ask about the reasons for this and offer support and advice. If there are no reasons why toilet training should not be attempted, advise parents or carer to toilet train their child. [1.15.2]

22.2.4.3 Suggest a trial of at least 2 nights in a row without nappies or pull-ups for a child with bedwetting who is under 5 years and has been toilet trained by day for longer than 6 months. Consider a longer trial in children:

- *who are older*
- *who achieve a reduction in wetness*
- *whose family circumstances allow the trial to continue. [1.15.3]*

22.2.4.4 Advise the parents or carers of child under 5 years with bedwetting that if the child wakes at night, they should use the opportunity to take him or her to the toilet. [1.15.4]

22.2.4.5 Consider further assessment and investigation to exclude a specific medical problem for children over 2 years who, despite awareness of toileting needs and showing appropriate toileting behaviour, are struggling to not wet themselves during the day as well as the night. [1.15.5]

22.2.4.6 Assess children under 5 years with bedwetting for constipation, in line with 'Constipation in children and young people' (NICE clinical guideline 99), as undiagnosed chronic constipation is a common cause of wetting and soiling in younger children.[1.15.6]

23 Support and follow-up for children with Bedwetting

23.1 Introduction

The evidence review searched for studies which considered if giving support and follow up during and / or after treatment impacts on the success of the treatment of bedwetting in children and young people. The evidence review did not identify any studies which considered the impact of support and follow up. Studies were identified which considered follow up of children, however the follow up was contact with the parent or child to assess if the child was still dry after successful treatment and did not consider how this phone call impacted on the success rate.

23.2 *What is the clinical and cost effectiveness of support and follow up care for children and young people under 19 years old who have bedwetting?; What is the clinical and cost effectiveness of support and follow up care for the parents and carers of children and young people under 19 years old who have bedwetting?*

23.2.1 Evidence review

No evidence was identified which considered the clinical effectiveness of support and follow up for children or families with nocturnal enuresis.

23.2.2 Evidence statements

No evidence was identified which considered the clinical effectiveness of support and follow up for children or families with nocturnal enuresis.

23.2.3 Evidence to recommendations

Relative values of different outcomes

The GDG considered the children and parents or carers starting treatment for bedwetting were seeking an outcome of sustained dryness. A number of different outcomes were used to capture this: the outcome of 14 consecutive dry nights, reduction in wet nights and the mean number of wet nights allow evaluation of the effectiveness of treatment. Follow up rates where available can indicate sustained dryness.

Trade off between clinical benefit and harms

No evidence found

Economic considerations

Follow-up and support both during and after treatment of bedwetting represents a cost to the NHS, one that has not been calculated in the published literature. It is unknown, based on the evidence review, how this follow-up and support improves outcomes of treatment, and thus it is difficult to determine whether the additional costs to the NHS are justified by the improved outcomes. However, the potential resource use needed to provide adequate follow-up and support to patients undergoing treatment was estimated from GDG opinion and incorporated in the economic modelling undertaken for this guideline. Results emerging from the modelling indicate that based on the assumptions made, 2 or 3 follow-up appointments to check progress during the first 3 months of a new treatment are likely to be cost-effective. For longer term treatment with pharmacological interventions, an appointment with a GP at least once every 6 months is also likely to be cost-effective.

Quality of evidence (this includes clinical and economic)

No direct evidence found

Other considerations

The GDG used evidence from professional experience and health economic analyses to develop the recommendations.

The GDG made recommendations about information children and parents receive and the importance of access to adequate support, particularly when using alarms. The GDG reported that it was common clinical practice to offer phone support to families which could be initiated by families where required.

23.2.4 Recommendations

See chapters on individual treatment methods

24 Network Meta-Analysis

24.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as previously presented) make it difficult to determine which intervention is most effect in the treatment of bedwetting. The challenge of interpretation has arisen for two reasons:

- Some pairs of alternative strategies have not been directly compared in a randomised controlled trial (for example, Dry Bed Training with alarm vs Desmopressin).
- There are frequently multiple overlapping comparisons (for example, alarm vs desmopressin, alarm vs imipramine and desmopressin vs imipramine), that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different interventions in order of efficacy, defined as the achievement of a full response without the recurrence of bedwetting after treatment discontinuation. The analysis also provided estimates of effect (with 95% credible intervals¹²) for each intervention compared to one another and compared to a single baseline risk. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates were used to parameterise treatment effectiveness of first line interventions in the de novo cost-effectiveness modelling presented in appendix G.

24.2 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials included in the clinical evidence review already presented in chapters 7 to 20. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and was undertaken in one of the populations of interest for the minimum required length of treatment) then it was included in the network meta-analysis. If the outcome, population or treatment length did not meet the inclusion criteria, then the study data was excluded from the network meta-analysis.

¹² Credible intervals are the Bayesian equivalent of confidence intervals and are based on the percentiles of the posterior distribution of the parameter of interest.

The interventions included were

Behavioural:

- Alarms
- alarm and information leaflets
- alarm and information CD
- dry bed training with an alarm
- dry bed training without an alarm
- retention control training and an alarm
- star charts
- stop start training
- retention control training with placebo

Pharmacological:

- desmopressin (intranasal and tablet)
- imipramine
- amitriptyline
- oxybutynin

Combination:

- desmopressin and amitriptyline
- desmopressin and oxybutynin
- imipramine and oxybutynin
- alarm and tablet desmopressin
- retention control training and desmopressin

Psychological:

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- psychotherapy
- play therapy
- a 3 step programme
- 3 step programme and motivational therapy

Alternative therapies:

- homotoxicological remedies

The details of these interventions can be found in the clinical evidence review chapters of the guideline.

24.3 Methods

To estimate the relative risks, we performed a hierarchical Bayesian network meta-analysis that simultaneously used all the relevant randomised controlled trial evidence from the clinical evidence review⁹⁴ – for details see appendix F. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination was derived only from randomised controlled trials that had that particular combination in a trial arm.

Data from all the relevant RCTs in the clinical review were included in the analysis. We produced 3 NMA models, each defined by their outcome measure and population. These are visually represented in figures 1a, 1b and 1c, respectively.

Network 1: Full response (bedwetting only)

- Evidence for patient populations explicitly identified as either mono-symptomatic or having only bedwetting.
- Evidence only for treatment periods of at least 12 weeks for enuresis alarms or behavioural interventions and at least 8 weeks for pharmacological interventions.

Network 2: Full response (bedwetting with possible daytime symptoms)

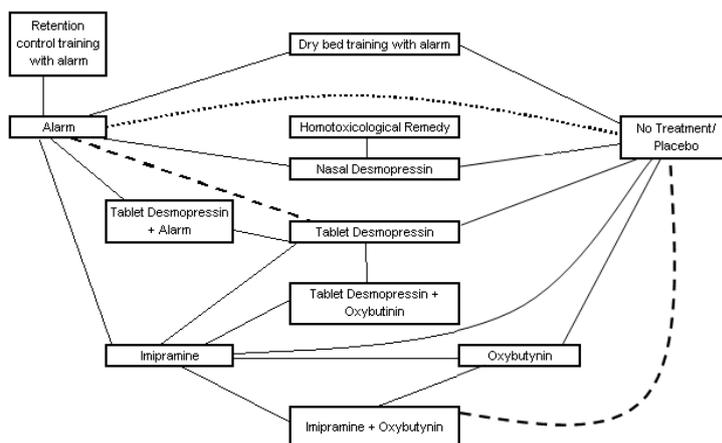
- Evidence for patient populations not positively identified as either mono-symptomatic or having only night time wetting (referred to as patients with bedwetting with possible daytime symptoms).

- Evidence only for treatment periods of at least 12 weeks for enuresis alarms or behavioural interventions and at least 8 weeks for pharmacological interventions.

Network 3: Recurrence of bedwetting at 6 months following discontinuation of treatment (bedwetting only)

- Evidence for patient populations explicitly identified as either mono-symptomatic or having only bedwetting.
- Evidence only for treatment periods of at least 12 weeks for enuresis alarms or behavioural interventions and at least 8 weeks for pharmacological interventions and with reports of experienced a recurrence of bedwetting within 6 months of successful treatment.

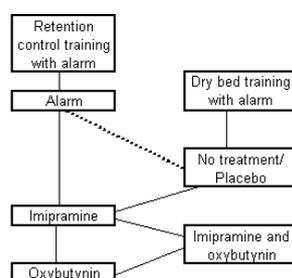
Figures 1a: Network 1: Full response for children with bedwetting only



Lines represent direct comparisons: solid lines indicate 1 study contributing to the results, dashed indicates 2 studies and dotted represents 3 studies.

Figure 1b: Network 2: Full response for children with bedwetting with possible daytime symptoms

Figure 1b: Network 3: Recurrence of bedwetting at 6 months following discontinuation of treatment for children with bedwetting only



Lines represent direct comparisons: solid lines indicate 1 study contributing to the results, dashed indicates 2 studies.

24.4 Results

Network 1 was composed of 10 studies including 798 patients. Network 2 was composed of 17 studies including 1360 patients. Network 3 was composed of 5 studies including 95 patients.

For each strategy, the results are given in terms of the relative risk (RR) compared to no treatment. We generated the no treatment baseline risk from data reported by Butler and Heron²⁸ from the Avon Longitudinal Study of Parents and Children (ALSPAC). Between the ages of 7.5 and 9.5 years, the ‘risk’ of achieving dryness without treatment was 10.34%. From the same data, the ‘risk’ of relapsing after achieving dryness without treatment was 0.6134%.

The results for network 1, summarised in table 1 and figure 2, show that combined alarm and desmopressin performs best overall with a relative risk of 8.519 (95% CI: 3.567 to 9.578) compared to no treatment. This was the most effective intervention in 41.16% of Markov chain simulations. Other effective interventions compared to no treatment include alarms, dry bed training with alarm, tablet desmopressin and combined tablet desmopressin and oxybutynin. Although the median point estimates of relative risk indicate a difference in effectiveness between these interventions, the 95% credible intervals are wide and all overlap.

Table 24-1: Effectiveness of interventions in network 1 compared to no treatment

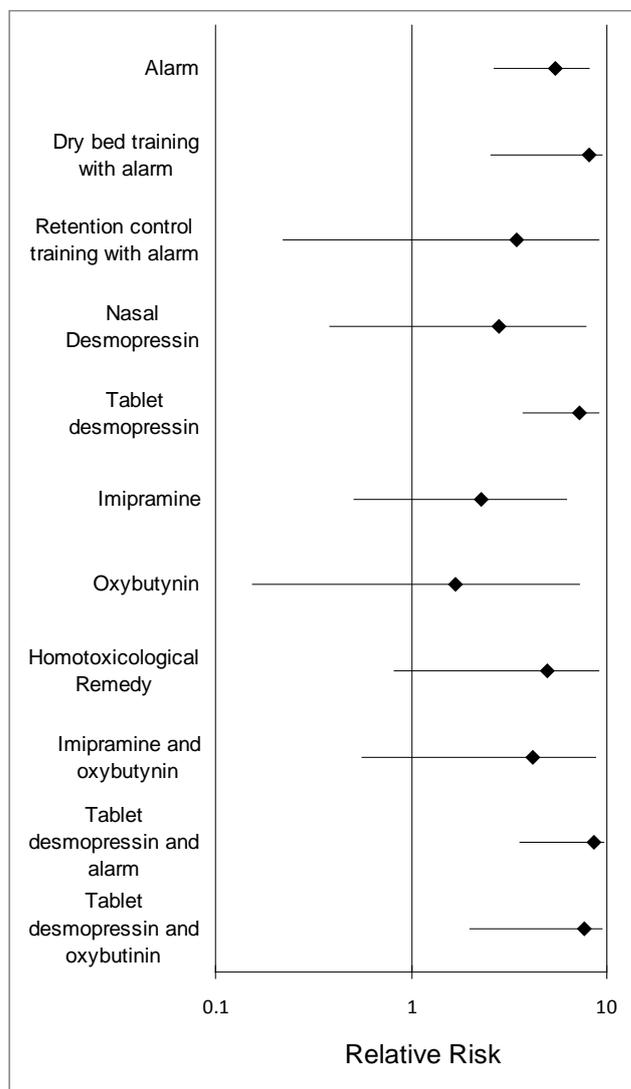
Interventions	Median relative risk (95% Credible Interval)	Probability intervention is most effective (%)
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Tablet desmopressin and alarm	8.519 (3.567 – 9.578)*	41.16
Dry bed training with alarm	8.116 (2.538 – 9.523)*	29.23
Tablet desmopressin and oxybutynin	7.640 (2.012 – 9.525)*	18.89
Tablet desmopressin	7.281 (3.727 – 9.109)*	3.22
Alarm	5.497 (2.633 – 8.079)*	0.11
Homotoxicological Remedy	4.969 (0.820 – 9.032)	2.7
Imipramine and oxybutynin	4.188 (0.561 – 8.737)	1.85
Retention control training with alarm	3.484 (0.224 – 9.031)	2.28
Nasal Desmopressin	2.785 (0.387 – 7.743)	0.35
Imipramine	2.259 (0.513 - 6.172)	0.01
Oxybutynin	1.696 (0.153 – 7.277)	0.23

Relative risk greater than 1 favours the intervention. *Statistically significant.

Figure 2: NMA 1: Intervention vs no treatment for full response for children with bedwetting only



The results for network 2, summarized in table 2 and figure 3, show that amitriptyline performs best overall with a relative risk of 9.514 (95% CI: 6.906 to 9.667) compared to no treatment. In 35.59% of Markov chain simulations, amitriptyline was the most effective treatment. Other interventions more effective than no treatment include alarms alone or with an informational leaflet or CD, dry bed training with alarm, stop start training, retention control training and alarm, retention control training, desmopressin, imipramine, 3 step programme with or without motivational therapy, desmopressin and retention control training, combined desmopressin and amitriptyline and combined desmopressin and oxytubynin. Although the median point estimates of relative risk indicate a

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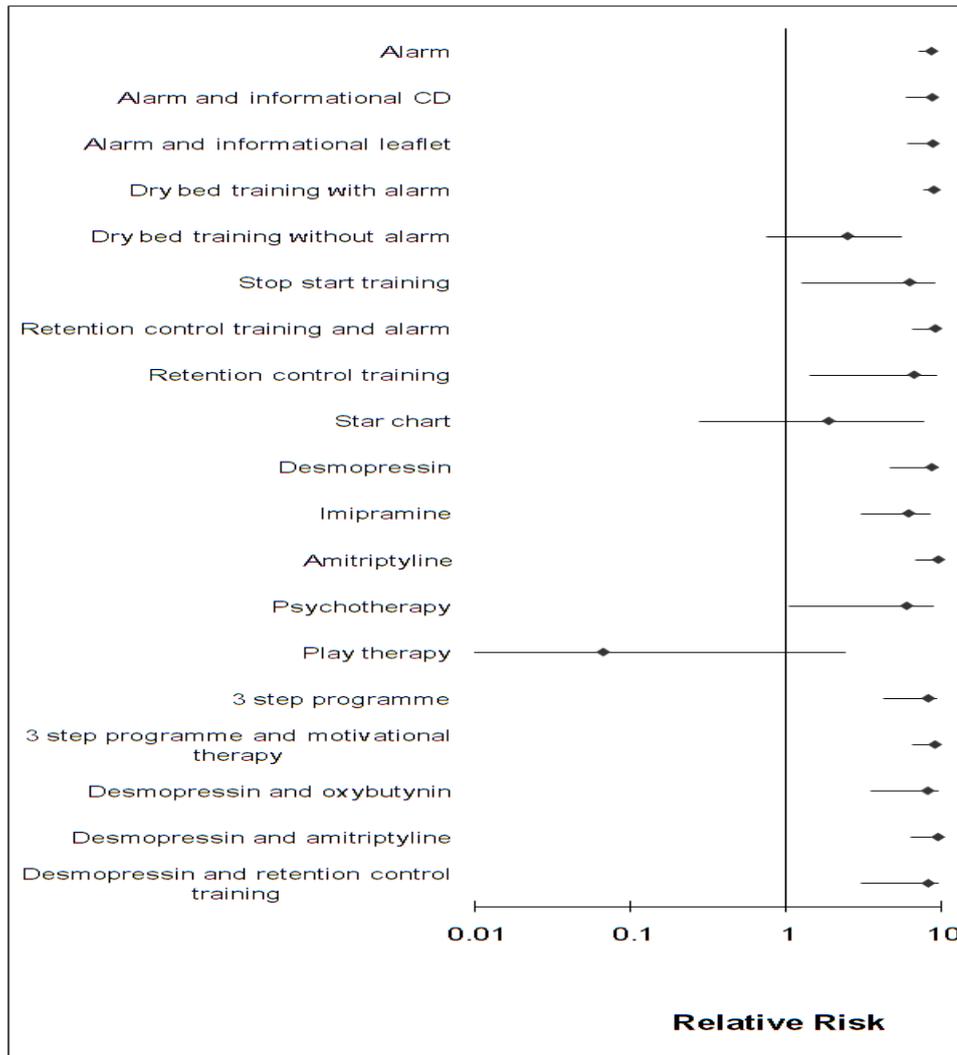
difference in effectiveness between these interventions, the 95% credible intervals all overlap. Notably, play therapy was the least effective intervention, appearing to be worse than no treatment. However, the 95% credible interval crossed 1 and therefore there is considerable uncertainty in this estimate of effect.

Table 24-2: Effectiveness of interventions in network 2 compared to no treatment

Interventions	Median relative risk (95% Credible Interval)	Probability intervention is most effective (%)
Amitriptyline	9.514 (6.906– 9.667)*	35.59
Desmopressin and amitriptyline	9.481 (6.444 – 9.667)*	26.92
Retention control training with alarm	9.114 (6.641 – 9.578)*	11.71
3 step programme and motivational therapy	9.070(6.555 – 9.594)*	9.80
Dry bed training with alarm	8.919 (7.736 – 9.319)*	2.73
Alarm and informational leaflet	8.770 (6.153 – 9.426)*	3.12
Alarm and informational CD	8.706 (6.047 – 9.406)*	2.36
Alarm	8.601 (7.294 – 9.103)*	0.07
Desmopressin and oxybutynin	8.141 (3.539 – 9.53)*	0.49
3 step programme	8.213 (4.251 – 9.479)*	0.61
Desmopressin	8.641 (4.681 – 9.569)*	0.27
Desmopressin and retention control training	8.198 (3.057 – 9.572)*	0.55
Stop start training	6.245 (1.267 – 9.085)*	0.20
Imipramine	6.149 (3.100 – 8.537)*	0
Psychotherapy	5.972 (1.068 – 8.977)*	0.16
Placebo and retention control training	6.664 (1.432 – 9.423)*	0.07
Star chart	1.891 (0.282 – 7.709)	0
Dry bed training without alarm	2.497 (0.754 – 5.528)	0
Play therapy	0.068 (0.004 – 2.407)	0

Relative risk greater than 1 favours the intervention. *Statistically significant.

Figure 3: NMA 2: Intervention vs no treatment for full response for children with bedwetting with possible daytime symptoms



The results for network 3, summarized in table 3 and figure 4, show that alarm performs best overall with a 96.36% relative risk reduction (RR = 0.0364, 95% CI: 0.004655 to 0.8397) compared to no treatment. Alarm was ranked as most effective in 7.55% of Markov chain simulations. Combined imipramine and oxybutynin had the largest median relative risk reduction of 98.9% (RR=0.01094) compared to no treatment, but the 95% credible interval crossed 1 and was therefore not statistically significant. The effectiveness of other interventions compared to no treatment did not reach statistical significance.

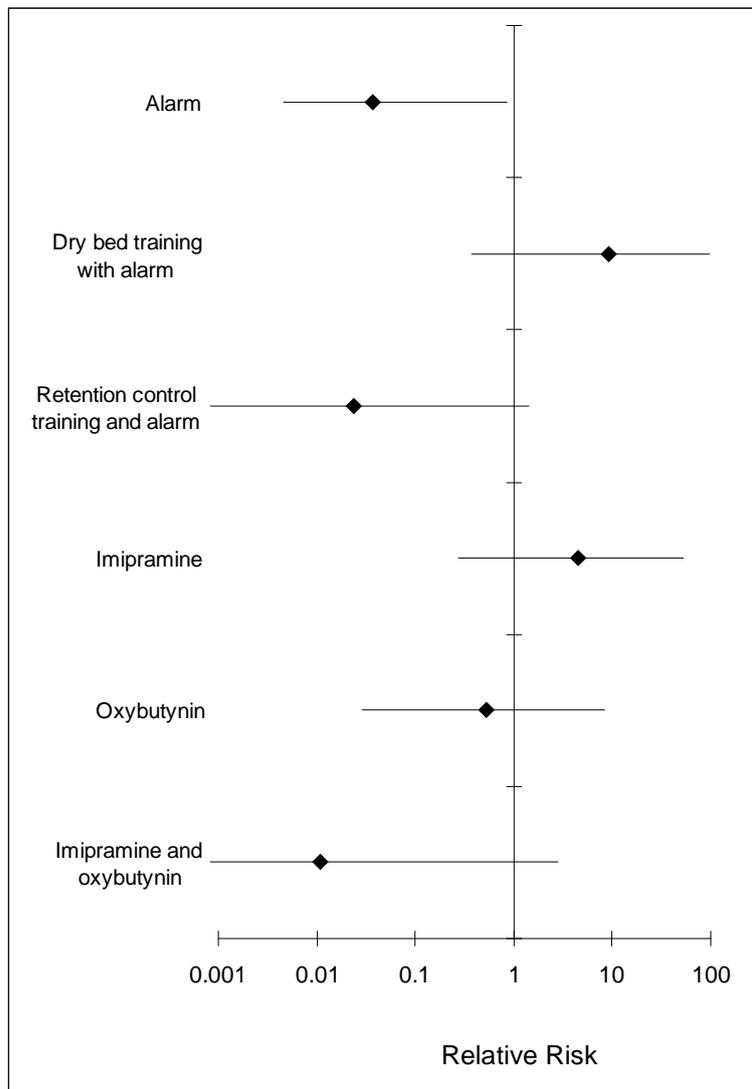
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Table 24-3: Probability of bedwetting recurrence at 6 months following discontinuation of treatment in network 3 compared to no treatment

Interventions	Median relative risk (95% Credible Interval)	Probability intervention is most effective (%)
Dry bed training with alarm	0.011 (0.000 – 2.764)	58.73
Retention control training with alarm	0.024 (0.001 – 1.400)	30.32
Alarm	0.036 (0.005 – 0.840)*	7.55
Imipramine and oxybutynin	0.523 (0.029 – 8.444)	3.19
Imipramine	4.566 (0.277 – 52.540)	0.04
Oxybutynin	9.279 (0.370 – 95.690)	0.04

Relative risk less than 1 favours the intervention. *Statistically significant.

Figure 4: NMA 3: Intervention vs no treatment for probability of bedwetting recurrence at 6 months following discontinuation of treatment



24.5 Discussion

This analysis allowed us to combine the findings from many of the different comparisons presented in the previous chapters. Using this approach we have been able to make comparisons between different interventions used in the treatment of bedwetting even when direct comparative data was lacking or the results gave inconsistent estimates of effectiveness.

Although there are many interventions that are clearly among the least effective and others that are demonstrably more effective than no treatment, the analysis does not show there to be a great deal of statistically significant difference between interventions such that one or several can be clearly identified as the most effective or among the most effective. Often, the interventions with the greatest median relative risk had wide confidence intervals and the interventions with a mid-range relative risk had narrower credible intervals. And, although the analysis was able to generate probabilities of a given intervention being the best treatment, defined as having the greatest relative risk compared to no treatment, the probability estimates illustrate the considerable uncertainty around which intervention is truly optimal.

Although the usefulness of the analysis has already been stated, it has several noteworthy limitations:

- The overall size and quality of the included RCTs was a problem in the review of direct comparisons and performing this network meta-analysis did not make this problem disappear. Small trials and fairly inconclusive direct evidence fed into the network meta-analysis and produced estimates of effect with very wide and overlapping credible intervals. Drawing firm conclusions based on the evidence remains difficult.
- Differing definitions of ‘full response’ and ‘experienced a recurrence of bedwetting’ between studies made the formation of networks of evidence slightly difficult. The GDG judged that some definitions of ‘full response’ and ‘experienced a recurrence of bedwetting’ were amalgamable thus allowing for the creation of a network. It is unclear as to whether these different definitions created or contributed to inconsistencies in the network. However, it is clear that if these outcome measures had not been combined, it is unlikely that any network meta-analysis could have been undertaken.
- Because of the heterogeneity in the methods, length of treatment, outcome measures and populations of the included studies we took several steps to try and reduce the impact this might have on our results. First, we split the studies into separate networks by population and defined minimum lengths of treatment by type of intervention. Second, we used a random effects model which estimates wider confidence intervals to account for study heterogeneity. Despite this, we believe that heterogeneity between studies contributed to inconsistency observed in network 1. This inconsistency weakens conclusions that can be made based on that particular network.

In addition to summarising the direct evidence into single measures of relative risk compared to no treatment, another aim of the NMA was to inform the effectiveness

parameters of first line treatments in the economic model built to evaluate the cost-effectiveness of different intervention sequences used in the treatment of bedwetting. Although not all of the interventions included in the NMA were ultimately included in the economic model, they collectively formed a network of evidence that was used to derive the best estimates of effect for those interventions that were included in the model.

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