NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Surveillance review consultation document

4-year surveillance review of CG111: Nocturnal Enuresis: The management of bedwetting in children and young people

Background information

Guideline issue date: October 2010
4 year review: October 2014

Surveillance review recommendation

Surveillance review proposal put to consultees:

The Nocturnal enuresis guideline should not be considered for an update at this time.

Main findings of the current 4 year surveillance review

An Evidence Update was produced for the guideline in 2012 and was used as a source of evidence for the review proposal. The Evidence Update considered new evidence from 13th November 2009 to 28th February 2012. The Evidence Update indicated that there is currently insufficient new evidence to invalidate the guideline recommendations.

For this 4 year surveillance review a search to identify new evidence was carried out for articles published between 28th February 2012 (the end of the search period for the Evidence Update) and 26th August 2014 to identify randomised controlled trials (RCTs) and systematic reviews. Input was also received through the Cochrane Incontinence Group to help identify relevant systematic reviews and RCTs. Relevant abstracts were then assessed. Clinical feedback was also obtained from members of the guideline development group (GDG) through a questionnaire survey. Two of the questionnaire responders were aware of evidence that would change the current guideline recommendations

and felt that CG111 Nocturnal Enuresis did require an update at this time. They stated that more clarity was needed regarding the age that a child can be expected to receive assessment for treatment. However, the guideline does not currently define a lower age limit and bedwetting is common in children under 5 years old and often spontaneously improves. Furthermore, treatments available for bedwetting are often not licensed or suitable for those under 5 years old. Due to this, the guideline provides separate recommendations for children under 5 years old with nocturnal enuresis. It was also stated that there could be reference to the inequality of access issue and the publication of a NICE-accredited commissioning guide by the paediatric continence services to address this. This commissioning guide provides support for the local implementation of NICE guidance through commissioning and should be read together with CG111. Of the remaining respondents, one was unsure if the guideline needed to be updated whilst one respondent marked not applicable. The GDG chair agreed with the decision not to currently update this guideline and discussions with the Cochrane Incontinence Group indicated that it may be more appropriate to review this guideline again in two years.

New evidence was identified for the current 4 year surveillance review relating to the following clinical areas within the Nocturnal Enuresis guideline.

<table>
<tr><th colspan="3">Clinical area: Assessment for children with bedwetting</th></tr>
<tr><td colspan="3">Q: 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?</td></tr>
<tr><th>Evidence summary</th><th>GDG/clinical perspective</th><th>Impact</th></tr>
<tr><td><u>Evidence Update (2012)</u>
No evidence identified.

<u>4 Year Surveillance Review (2014)</u>
No evidence identified.</td><td>A GDG member highlighted that there have been a number of studies on the value of investigations such as bladder ultrasound which suggest their usefulness. However, no details of these studies were provided.</td><td>The clinical feedback will not currently impact on CG111 because no study details were provided.</td></tr>
<tr><th colspan="3">Clinical area: Bladder training and retention control training for the management of bedwetting</th></tr>
<tr><td colspan="3">Q: 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?</td></tr>
<tr><th>Evidence summary</th><th>GDG/clinical perspective</th><th>Impact</th></tr>
<tr><td><u>Evidence Update (2012)</u>
No evidence identified.

<u>4 Year Surveillance Review (2014)</u>

Simple Behavioural Interventions</td><td>None identified through GDG questionnaire.</td><td>The new evidence for simple behavioural interventions suggests that these interventions are not as effective as enuresis alarms. As such, this new evidence is supportive of the current guideline recommendation which states: Do not use strategies that recommend the interruption of</td></tr>
</table>

A Cochrane review[1] assessed the efficacy of simple behavioural interventions in children up to the age of 16 with nocturnal enuresis. Sixteen randomised and quasi-randomised trials were included (n=1643). The results showed that simple behavioural interventions were superior to no active treatment but were not superior to enuresis alarms and some drug therapies, such as imipramine and amitriptyline. **Nonmonosymptomatic Enuresis** An RCT[2] compared behavioural modification plus pelvic floor muscle training to behavioural modification plus oxybutynin. Children (n=47) with nonmonosymptomatic enuresis were randomised to either the oxybutynin group or to pelvic floor exercises. The results showed that there was a significant difference between groups at months two and three in the number of dry nights, with the pelvic floor muscle training groups showing more dry nights than the oxybutynin group. The authors concluded that pelvic floor muscle training was more effective than oxybutynin.		urinary stream or encourage infrequent passing of urine during the day (1.15.1). Limited new evidence from a small study indicates that pelvic floor muscle training is beneficial for nonmonosymptomatic nocturnal enuresis. Whilst Sphincter muscle exercises were considered in the guideline, the original GDG did not make any recommendations on these due to the inadequate descriptions of the interventions provided by the included trials. At present, only a small study on this area was identified and this is unlikely to provide sufficient evidence to warrant an update regarding this intervention. More large trials are needed.
Clinical area: Enuresis Alarms in the management of bedwetting		
Q: What is the clinical and cost effectiveness of enuresis alarms for children and young people under 19 years old who have bedwetting?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update 2012</u> A UK based multicentre RCT[3] was identified that compared desmopressin with enuresis alarm in 251 children aged between 5 to 16 years who had severe primary monosymptomatic nocturnal enuresis. The results showed that there was no significant difference in response rates between	Two GDG members highlighted the increasing availability of enuresis alarms and indicated that cheaper alarms are now available. Clinical feedback suggests that the	The Evidence Update concluded that treatment with desmopressin or alarm is equally effective in reducing the number of wet nights. Furthermore, the new evidence identified during this surveillance review suggests that enuresis alarms, desmopressin and a combination are all efficacious in treating nocturnal enuresis.

the two groups at the end of treatment. 4 Year Surveillance Review (2014) An RCT[4] was identified that investigated the efficacy of enuresis alarm, desmopressin and a combination for the treatment of children with monosymptomatic nocturnal enuresis (n=136). Authors concluded that all three treatments were effective in treating nocturnal enuresis in children. Desmopressin and combination therapy produced an immediate reduction in wetting frequency. However, relapse rates were common for those receiving desmopressin. Enuresis alarms provided gradual effects that persisted post treatment. Furthermore, their effect was better over the long term compared to combined therapy.	guideline recommendations are being interpreted such that alarms are considered the only initial treatment. With regards to the interpretation of guideline recommendations, users of NICE guidance should refer to the NICE pathway which brings together all of the nocturnal enuresis recommendations in a clear pathway that is easy to follow.	However, whilst both desmopressin and combination therapy provide immediate effects, enuresis alarms provide more gradual effects. These gradual effects persist post treatment and in the long term. In addition, the effect of alarms was better over the long term compared to combined therapy. Taken together, the new evidence is consistent with current recommendations in CG111 which suggest offering either alarms or desmopressin as initial treatment depending on the needs and circumstances of the family. Combination treatments are recommended in CG111 as a second line option (1.9.1 and 1.11.2). The new evidence is supportive of this as it suggests that whilst combination therapies are beneficial in the short term, over the long term the effect of alarms is better. Clinical feedback indicated that alarms are now cheaper than when the guideline was first developed. This is supportive of the current guideline which sees enuresis alarms as the most cost-effective treatment. As such, the clinical feedback is unlikely to impact on guideline recommendations.
Clinical area: Desmopressin and the management of bedwetting		
Q: What is the clinical and cost effectiveness of desmopressin for children and young people under 19 years who have bedwetting?		
Evidence summary	**GDG/clinical perspective**	**Impact**

<u>Evidence Update (2012)</u> No evidence identified. <u>4 Year Surveillance Review (2014)</u> **Desmopressin formulation.** A post-hoc analysis[5] was identified that investigated the efficacy of desmopressin melt compared to tablet. Two hundred and twenty-one children aged 5 to 15 years were randomised to either melt/tablet treatment sequence or tablet/melt. Results showed that the probability of being a responder was improved with melt compared to tablet formulation. Furthermore, patient compliance was increased by switching to melt from tablet. **Withdrawal of desmopressin** An RCT[6] investigated whether a structured withdrawal programme from a sublingual formulation of fast-melting oral desmopressin lyophilisate (MELT) was superior to sudden withdrawal. One hundred and three children with monosymptomatic nocturnal enuresis aged between 5 and half years to 14 years were randomised. At one month, relapse rates were 47.83% in the structured program group and 45.83 % in the sudden withdrawal group. **Other drugs** An updated Cochrane review[7] assessed the efficacy of drugs other than desmopressin and tricyclics on nocturnal enuresis in children up to the age of 16 years. Forty randomised and quasi-randomised trials were included. Results showed	None identified through GDG questionnaire.	The GDG were originally uncertain about the results from studies investigating melt versus tablet desmopressin when considering for inclusion in the original guideline. They thought that it would be inappropriate to recommend a specific route for desmopressin and instead thought it best to recommended desmopressin in general. However, the new evidence suggests that melt formulation improves the probability of being a responder and improves compliance compared to tablet formulation. Nonetheless, the new evidence is currently limited to a post-hoc analysis and so more research is needed before considering more detailed guidance on different formulations of desmopressin. The new evidence on withdrawal of desmopressin indicated that there was no difference in relapse rates between sudden withdrawal and structured withdrawal. Currently, the guideline recommends gradually withdrawing desmopressin rather than suddenly stopping it for bedwetting recurrence following response to previous treatment courses. The new evidence is not consistent with this recommendation. However, the evidence is from a small study and from an assessment of the abstract, it is not possible to determine whether the included children had or had not experienced recurrence of bedwetting following response to previous treatment courses. As such, we do not know if these results apply to children withdrawing from their first use of desmopressin or to those withdrawing from desmopressin after relapse from previous treatments. Therefore, it is unlikely that the new evidence will impact on this

that indomethacin, diazepam, mestorelone and atomoxetine were beneficial compared to placebo. However, when compared to desmopressin, indomethacin and diclofenac were not as effective. None of the drugs were found to be effective in reducing relapse rates. For drugs versus drugs, combination therapy with imipramine and oxybutynin was more effective that imipramine monotherapy. When compared to behavioural interventions enuresis alarms were found to be more beneficial than amphetamine, oxybutynin and oxybutynin plus holding exercises.		recommendation. The new evidence on other drugs showed that they were not as effective as desmopressin or alarms. Therefore, this evidence is supportive of current recommendations which propose enuresis alarms and desmopressin as first line treatment.
Clinical area: Anticholinergic medication for the management of Nocturnal Enuresis		
Q: What is the clinical and cost effectiveness of anticholinergic medication for children and young people under 19 years who have nocturnal enuresis?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> A double-blind RCT[8] was identified that examined the efficacy of desmopressin plus oxybutynin compared to desmopressin plus placebo in children aged between 6 to 13 years with monosymptomatic nocturnal enuresis (n=206). At the end of treatment, desmopressin plus oxybutynin had more full and partial responders than desmopressin plus placebo. However, this study used shorter treatment regimens than those currently recommended in CG111. <u>4 Year Surveillance Review (2014)</u> No evidence identified.	None identified through GDG questionnaire.	The evidence from the Evidence Update is consistent with current guideline recommendations which recommend the addition of an anticholinergic for partial or non-responders to initial desmopressin treatment.
Clinical area: Tricyclic medication and the management of bedwetting		
Q: What is the clinical and cost effectiveness of tricyclic medication for children and young people under 19 years who have bedwetting?		

Evidence summary	GDG/clinical perspective	Impact
<u>Evidence Update (2012)</u> No evidence identified. <u>4 Year Surveillance Review (2014)</u> **Children with ADHD** An RCT[9] examined the efficacy of nortriptyline for treating nocturnal enuresis in 43 children aged 5 to 14 years who had attention deficit hyperactivity disorder (ADHD). Children were randomised to methylphenidate plus nortriptyline or methylphenidate plus placebo. It was found that nortriptyline was superior to placebo at decreasing the incidence of nocturnal enuresis during treatment. However, nocturnal enuresis was found to relapse after nortriptyline was stopped.	None identified through GDG questionnaire.	For children with ADHD, the new evidence suggested that nortriptyline was efficacious in reducing nocturnal enuresis in this population. However, patients were found to relapse once treatment had stopped. Nortriptyline was considered in the guideline but only imipramine is recommended. This is because the original GDG thought that it was the tricyclic of choice since it is the most commonly used drug for this indication and there is more clinical experience of its use. Furthermore, the case fatality rate is considered to be higher with other tricyclics. Currently, the new evidence is unlikely to impact on the current recommendations since only one small study was identified. This study is unlikely to provide sufficient evidence to warrant an update of this guideline area. Larger trials of the use of this tricyclic in children with nocturnal enuresis are needed before considering an update of the guideline recommendations.
Clinical area: Treatment for children who do not respond to initial treatment with desmopressin and/or enuresis alarms for the management of bedwetting.		
Q: 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?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update 2012</u> A crossover RCT[10] investigated the efficacy of both enuresis alarm and desmopressin as first and second line treatments in children aged 6 to	None identified through GDG questionnaire.	The evidence identified in the Evidence Update is consistent with the current recommendations in CG111 which state that alarm and desmopressin are equally effective in the first-line and should be

15 years with monosymptomatic nocturnal enuresis (n=104). The results showed that desmopressin and alarm were equally effective in reducing wet nights as a first line treatment. There was also no significant difference between groups in response rate. For second line treatment, there was no significant difference in the reduction of wet nights between the two groups and no significant difference in the rate of successful responses between the alarm and desmopressin groups. <u>4 Year Surveillance Review (2014)</u> No evidence identified.		offered based on family preferences. The evidence is also consistent with the recommendation which states that following failure of first-line alarm treatment, treatment with desmopressin can be effective. The Evidence Update also found that alarms may be a potentially effective second line treatment following the failure of desmopressin. However, no new evidence in this area was identified through the 4 year surveillance review. Further research is need in this area before considering for inclusion in the guideline.
Clinical area: Under 5 year olds and management of bedwetting		
Q: In children under 5 years old with nocturnal enuresis, are there any preventive, prediction or treatment options which should be considered?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> An RCT[11] was identified that investigated the effects of behavioural interventions for bedwetting in 4 to 5 year old children with monosymptomatic nocturnal enuresis (n= 570). Patients were randomised to lifting with password, lifting without a password, award stars on a chart for dry nights with a reward given after a preset number of dry nights or no intervention. Results showed that only those using lifting without a password showed a significantly higher rate of dryness compared to controls at the end of the six month intervention period. At further follow-up (mean 2.6 years) there was no significant difference in dryness rate between any of the groups. The lack of long-term adverse outcomes with this intervention is potentially important since lifting is	A GDG member thought that there should be more clarity within the guideline on the age that a child can be expected to receive treatment for nocturnal enuresis.	The Evidence Update suggested that due to the limitations of the study it is unlikely to impact on NICE CG111. However, they do state that the results from the long-term follow-up indicate that lifting does not appear to impact on the tendency of children to naturally become dry as they get older which has previously been a concern. With regards to the clinical feedback, the guideline does not currently define a lower age limit. However, bedwetting is common in children under 5 years old and often spontaneously improves. Furthermore, treatments available for bedwetting are often not licensed or suitable for those under 5 years old. Due to this, the guideline provides separate recommendations for children under 5 years old with nocturnal enuresis.

frequently reported as a management strategy. Indeed, one study[12] involving questionnaires found that about 70% of parents with children (7.5 years old) with nocturnal enuresis had used lifting strategies at some point in the past. <u>4 Year Surveillance Review (2014)</u> No evidence identified.		
Clinical area: Research Recommendation		
Q: What is the effectiveness of complementary therapies (acupuncture and hypnotherapy) for reducing the number of wet beds and improving self-esteem in children and young people who wet the bed, when they are used independently or in conjunction with conventional treatments?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> **Complementary Therapies** A Cochrane review[13] assessed the effect of several complementary therapies on nocturnal enuresis in children. It included 24 RCTs which looked at hypnosis, psychotherapy and counselling, acupuncture, chiropractic, diet or food restriction, medicinal herbs and faradisation. The review found some indication of an effect for acupuncture, hypnosis, medicinal herbs, psychotherapy and chiropractic however, the results were based on single trials. **Laser acupuncture** Two RCTs on laser acupuncture were identified. The first[14] assessed laser acupuncture in children aged 5 to 16 years with monosymptomatic nocturnal enuresis (n=91). Children were randomised to laser acupuncture or placebo acupuncture with a nonlaser light source. Results	None identified through GDG questionnaire.	The Evidence Update concluded that the evidence on complementary therapies did not support the use of these interventions. It was suggested that more methodologically rigorous RCTs are needed before such interventions can be considered for inclusion in the guideline. For laser acupuncture, the evidence was considered insufficient to currently impact on CG111. The Evidence Update suggested that further research into laser acupuncture is needed, especially with regards to laser acupuncture compared to standard interventions.

at six months showed that those in the laser acupuncture group experienced a reduction in mean number of weekly bed wetting episodes and a significantly higher complete improvement (defined as no bed wetting episodes). The second RCT[15] randomised 31 children (aged 7 to 11.8 years) with monosymptomatic nocturnal enuresis to three groups: laser acupuncture, placebo acupuncture without laser light but with skin contact and placebo acupuncture without laser light and without skin contact. No significant differences were observed between the three groups for maximal volume, voiding frequency, enuresis frequency or nocturnal urine production. <u>4 Year Surveillance Review (2014)</u> No evidence identified.		
Clinical area: Treatment		
Area not currently covered in the guideline		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> No evidence identified. <u>4 Year Surveillance Review (2014)</u> **Melatonin** An RCT[16] was identified that looked at the effect of exogenous melatonin in children with therapy-resistant monosymptomatic nocturnal enuresis. Twenty four children were randomised to synthetic melatonin or placebo. The authors found no change in enuresis frequency or in the sleep-wake cycle in either group.	None identified through GDG questionnaire.	Insufficient evidence on the effectiveness of melatonin was found. This was because the included study was small and it found no difference between melatonin and placebo in enuresis frequency. As such, the new evidence is unlikely to impact on CG111. Evidence on the effectiveness of parasacral transcutaneous electrical nerve stimulation indicated that this intervention lead to significantly less wet nights compared with control. However, as this was a small scale study, more studies are needed so that firm conclusions about the usefulness of these interventions can be drawn.

Electrical Nerve Stimulation An RCT[17] assessed the effectiveness of parasacral transcutaneous electrical nerve stimulation for the treatment of monosymptomatic primary nocturnal enuresis. Children (n=45) older than six years old were randomised to behavioural therapy plus ten sessions of parasacral transcutaneous electrical nerve stimulation or to behavioural therapy alone. Results showed a significantly greater increase in dry nights in the intervention group compared to the control group. Furthermore, at the end of treatment the rate of wet nights was found to be 49.5% in the control group but 31.2% in the intervention group. This was a statistically significant difference.		

For the following areas of the guideline no new evidence was identified:

- Impact of bedwetting on children and young people and their families
- Patient choice in children and young people with bedwetting
- Dry bed training for the management of bedwetting
- Fluid and diet restriction for the management of bedwetting
- Lifting and waking in the management of bedwetting
- Star Charts in the management of bedwetting
- Dose escalation in the management of bedwetting
- Treatment for children who have recurrence of bedwetting after previous successful treatment for bedwetting.
- Psychological treatments for the management of bedwetting
- Information and Educational interventions for the management of bedwetting
- Alternative treatments for the management of bedwetting
- Support and follow-up for children with bedwetting

Ongoing research

A GDG member highlighted an ongoing trial looking at risk factors and outcome factors for children and young people with enuresis (ROCCA study). Analysis and publication are due in 2016. No other details were provided. Four other ongoing trials were identified by the Cochrane Incontinence Group. In the first study, children with nocturnal enuresis (n=60) have been recruited into an Iranian RCT (IRCT201301117892N4) which compares oxybutynin plus desmopressin to desmopressin alone. A completion date for this study is not provided. The second RCT is also being conducted in Iran (IRCT138801161323N3). However, this study compares desmopressin with interferential currents therapy in children with nocturnal enuresis (n=75).The third ongoing study recruited 150 children with nocturnal enuresis and randomised them to imipramine, desmopressin or oxybutynin (IRCT138807042503N1). No completion information is provided for this study. In the last ongoing study one hundred children with monosymptomatic nocturnal enuresis will be randomised to tolterodin plus desmopressin or to desmopressin and placebo (IRCT2012090610758N1). No completion date is provided for this study. The Cochrane Incontinence Group also stated that it is currently updating three of its reviews on nocturnal enuresis which are likely to be completed in December 2014. These will be assessed for inclusion at the next surveillance review.

Anti-discrimination and equalities considerations

The GDG indicated that children and young people are not receiving the treatment/services specifically laid out in the guideline. Furthermore, the GDG highlighted a 2014 FOI survey of current inequalities in access to paediatric continence services in England. Access inequalities in paediatric continence services are addressed in a commissioning guide. This provides support for the local implementation of NICE guidance through commissioning and should be read together with CG111.

Conclusion

Through the 4 year surveillance review of CG111 no new evidence which may potentially change the direction of guideline recommendations was identified. The proposal is not to update the guideline at this time.

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