NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Recommendation for Guidance Executive (post-consultation)

Clinical guideline
CG111: Nocturnal Enuresis: The management of bedwetting in children and young people.

Publication date
October 2010

Surveillance report for GE (post-consultation)
December 2014

Surveillance recommendation
GE is asked to consider the following proposal which was consulted on for two weeks:

- The clinical guideline CG111: Nocturnal enuresis should not be considered for an update at this time.

Key findings

			Potential impact on guidance	
			Yes	**No**
Evidence identified from Evidence Update				✓
Evidence identified from literature search				✓
Feedback from Guideline Development Group			✓	
Anti-discrimination and equalities considerations				✓
No update	CGUT update	Standard update	Transfer to static list	Change review cycle
✓				

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Centre for Clinical Practice – Surveillance Programme

Surveillance review of CG111: Nocturnal Enuresis: The management of bedwetting in children and young people

Recommendation for Guidance Executive (post consultation)

Background information

Guideline issue date: 2010
4 year review: 2014

NCC: National Clinical Guidelines Centre

Four year surveillance review

1. 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.

2. The literature search for this 4 year surveillance review was carried out 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. Relevant abstracts were assessed and clinical feedback was obtained from members of the guideline development group (GDG) through a questionnaire survey. Half of the questionnaire respondents thought that CG111: Nocturnal Enuresis did need to be updated. 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. The GDG members also stated that there could be reference to the current inequalities in access to paediatric continence services 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. The GDG chair agreed with the decision not to currently update this guideline.

3. As part of this surveillance review we actively engaged with the Cochrane Incontinence Group. The group helped to identify relevant systematic reviews and RCTs and provided feedback on the surveillance review proposal. Discussions with the Cochrane Incontinence Group indicated that it may be more appropriate to review this guideline again in two years.

4. No new evidence was identified through the literature search which would invalidate the guideline recommendations.

Ongoing research

5. 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 has 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.

Anti-discrimination and equalities considerations

6. A GDG member stated that a 2014 survey provided evidence of current inequalities to access to paediatric continence services. No further details were provided.

Implications for other NICE programmes

7. A Quality Standard for Nocturnal Enuresis (QS70) was issued in September 2014.

8. A no to update decision is unlikely to impact on any of the Quality Statements within the Quality Standard.

Summary of stakeholder feedback

9. Stakeholders were consulted on the following proposal over a two week consultation period:

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

10. In total, ten stakeholders commented on the surveillance review proposal recommendation during the two week consultation period. The table of stakeholder comments can be viewed in Appendix 1. Eight stakeholders provided comments on the surveillance review proposal and the remaining two stakeholders stated that they had no substantive comments to make.

11. Of the eight stakeholders that provided comment, four agreed that CG111 did not need to be updated whilst four stakeholders disagreed.

12. The following is a summary of the general comments made by the stakeholders that disagreed with the surveillance review proposal:

13. Clarity of first line treatment recommendations.
Four stakeholders stated that further clarity was needed around the recommendations for first line treatment. They stated that many clinicians have misinterpreted the recommendations to mean that all children should be tried on an alarm first and should only commence desmopressin if this fails. However, CG111 clearly states: Consider whether or not it is appropriate to offer alarm or drug treatment, depending on the age of the child or young person, the frequency of bedwetting and the motivation and needs of the child or young person and their family (1.4.5). Furthermore, CG111 recommends that alarms should be used as first line treatment in those whose bedwetting has not responded to advice on fluids, toileting or an appropriate rewards system unless they are considered undesirable by the child, young person or parent/ carer or are considered inappropriate (where bedwetting is infrequent, the parent/carers are having emotional difficulty coping with the burden of bedwetting

or where the parents/carers are expressing anger, negativity or blame towards the child or young person) (1.8.1). In these cases, desmopressin should be offered (recommendation 1.10.1).

However, for interpretation of the guidelines, users should refer to the relevant NICE pathway as these bring together recommendations in an easy to follow manner.

14. Formulation of Desmopressin.

Four stakeholders stated that adequate evidence was now available to provide guidance to clinicians about formulations of desmopressin. In particular they suggested that the melt formulation is the better option when treating children with bedwetting and highlighted five studies. Of these five studies, one was already included in this surveillance review. This was a post-hoc analysis of 221 patients from a short-term study. As this study was the only study identified during this surveillance review it was concluded that the evidence was currently limited and that further, longer term larger RCTs are needed before detailed guidance on desmopressin formulation can be considered. Another of the highlighted studies was included in the original guideline and this looked at desmopressin melt versus tablet. However, the GDG noted that the study was designed to assess the impact of patient choice and was not designed to evaluate the difference in effectiveness of the two formulations. Two of the highlighted studies were published before the search period of this surveillance review and so would not have been included. The remaining study was not identified in the literature search for this surveillance review. However, an assessment of the abstract indicated that this study is a pharmacokinetics study. As it does not address the question of which formulation is the most efficacious and as is not an RCT it does not impact on the guideline recommendations.

15. Assessment of children with bedwetting.

One stakeholder stated that many children are seen in an enuretic clinic which means that often any underlying constipation is neither identified nor treated. This is important since resolving underlying constipation can help to resolve urinary tract symptoms. The stakeholder highlighted three studies. Currently, CG111 does recommend considering assessment, investigation and/or referral when bedwetting is associated with comorbidities or other risk factors such as constipation and/or soiling. Furthermore, the guideline recommends that children or young people with soiling or constipation should be investigated and treated in line with the Constipation in children guideline (CG99). Failure to follow these guideline recommendations is an implementation issue and should be addressed at the local level. With regards to the highlighted references, all of the studies were published before the search period of this surveillance review and so would not have been included.

Conclusion

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

Mark Baker – Centre Director
Sarah Willett – Associate Director
Louise Hartley – Technical Analyst

Centre for Clinical Practice
December 2014

Appendix 1 Surveillance review consultation

Surveillance review consultation comments table
21 November 2014 – 5 December 2014

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
GDG member	Yes	None I think the comments in the surveillance review are valid		Thank you for your comment.
Digital Assessment Service, NHS Choices	Agree			Thank you.
Royal College of Paediatrics and Child Health	Agree	None		Thank you.
Department of Health			The Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
NHS England			I wish to confirm that NHS England has no substantive comments to make regarding this consultation.	Thank you for your comment.
ERIC	Agree			Thank you for your comment

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
(Education & Resources for Improving Childhood Continence)				
PromoCon	Disagree Clinical area: Enuresis Alarms in the management of bedwetting	Clarity of first line treatment recommendations	Although it is recognised that alarm treatment is successful for those children for whom it has been deemed appropriate the current NICE guidance appears to give the wrong message regarding their use unless the initial treatment recommendations are read within the context of the complete guideline. Alarm treatment is recommended as first line treatment for children with bedwetting only if deemed appropriate and desirable. However many clinicians have misinterpreted those recommendations to mean that ALL children have to be tried on an alarm first and only if that fails should they commence desmopressin. This means that not only are often limited resources (ie alarms) being used inappropriately leading to treatment failures but also	Thank you for your comment. We are sorry that there is a view that the guideline has been misinterpreted. However, CG111 clearly states: Consider whether or not it is appropriate to offer alarm or drug treatment, depending on the age of the child or young person, the frequency of bedwetting and the motivation and needs of the child or young person and their family (1.4.5). The guideline also states in recommendation 1.8.1 that alarms should be first line treatment in those whose bedwetting has not responded to advice on fluids, toileting or an appropriate rewards system unless they are considered undesirable by the child, young person or parent/ carer or are considered inappropriate. In particular where bedwetting is infrequent, the parents/carers are

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
			those children for whom the alarm is suitable are having to go on, often long, waiting lists until an alarm becomes available for them to use	having emotional difficulty coping with the burden of bedwetting or where the parents/carers are expressing anger, negativity or blame towards the child or young person. At present, we do not believe that the wording of these recommendations needs clarification and allows clinicians options for treatment choice based on judgement and discussions with the family. However, for interpretation of the guideline, 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.
	Clinical area: Assessment for children with bedwetting	Many children are seen in 'enuretic' clinics only which means that often they do not undergo the comprehensive assessment that includes both bladders and bowels	NICE clearly states that any assessment should be comprehensive and include excluding any underlying problems such as constipation. However little emphasis is made regarding the importance of this within the guideline and as a result many children are seen in 'enuresis' clinics only. This means that often any	Thank you for your comment and for highlighting references for this consultation. All of the studies highlighted were not identified through the literature search because they were published before the search period of this surveillance review (28/12/12 to 26/8/14) and so

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
			underlying constipation is neither identified nor treated - despite the evidence that resolving any underlying constipation can help resolve urinary tract symptoms in up to 50% of all cases (Bael et al 2007, Akyoll et al 2007, Halachmi et al 2008) Functional urinary and fecal incontinence in neurologically normal children: symptoms of one 'functional elimination disorder'? Bael AM, Benninga MA, Lax H, Bachmann H, Janhsen E, De Jong TP, Vijverberg M, Van Gool JD; European Bladder Dysfunction Study and EU#BMH-CT. BJU Int. 2007 Feb;99(2):407-12. Epub 2006 Oct 11. An important issue in the management of elimination dysfunction in children: parental awareness of constipation. Akyol I, Adayener C, Senkul T, Baykal K, Iseri C.	have not been considered as part of this surveillance review. The guideline does recommends that assessment, investigation and/or referral should be considered when bedwetting is associated with comorbidities and other risk factors such as constipation and/or soiling. Furthermore, it states that children or young people with soiling or constipation should be investigated and treated in line with the Constipation in children guideline (CG99). Failure to follow these guideline recommendations is an implementation issue that should be addressed at the local level. However, for interpretation of the guideline, pathways for both nocturnal enuresis and constipation should be referred to as these bring together recommendations in an easy to follow manner.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
			Clin Pediatr (Phila). 2007 Sep;46(7):601-3. Epub 2007 May 23 The impact of constipation on the urinary tract system. Halachmi S, Farhat WA. Int J Adolesc Med Health. 2008 Jan-Mar;20(1):17-22. Review.	
	Clinical area: Desmopressin and the management of bedwetting	The use of Melt formulation of desmopressin is clearly more child friendly – particularly those with special needs who may have difficulties swallowing	There is now increased emerging evidence that the melt formulation of desmopressin is the better option when treating children with bedwetting. This is due to the increased bioavailability within the melt resulting in the children requiring a lower dose and the melt formulation means it is easier and more acceptable to take and does not require a drink to administer. Desmopressin melt improves response and compliance compared with tablet in treatment of primary monosymptomatic nocturnal enuresis. Juul KV1, Van Herzeele C, De Bruyne P, Goble S, Walle JV, Nørgaard JP.	Thank you for your comment. Thank you for highlighting references. The study by Juul et al. was identified and included in this 4 year surveillance review. The study by Lottman was published before the search period of this surveillance review. However, this study was included as evidence in the original guideline but the GDG noted that the study was designed to assess the impact of patient choice and was not designed to evaluate the difference in effectiveness of the two formulations. The study by De Bruyne was not identified in the literature search for this surveillance review. However, an assessment of the abstract indicated that this study is a pharmacokinetics

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
			Eur J Pediatr. 2013 Sep;172(9):1235-42. Desmopressin melt improves response and compliance compared with tablet in treatment of primary monosymptomatic nocturnal enuresis. Juul KV1, Van Herzeele C, De Bruyne P, Goble S, Walle JV, Nørgaard JP. Eur J Pediatr. 2013 Sep;172(9):1235-42 A randomised comparison of oral desmopressin lyophilisate (MELT) and tablet formulations in children and adolescents with primary nocturnal enuresis. Lottmann H1, Froeling F, Alloussi S, El-Radhi AS, Rittig S, Riis A, Persson BE. Int J Clin Pract. 2007 Sep;61(9):1454-60. Epub 2007 Jul 26. Pharmacokinetics of desmopressin administered as tablet and oral lyophilisate formulation in children with	study. As this study does not address the question of which formulation is the most efficacious and is not an RCT it does not currently impact on the guideline recommendations. During this surveillance review we found limited evidence comparing desmopressin melt with tablet formulation as only one post-hoc analysis was identified (Juul et al.). More research into the efficacy of melt compared to tablet formulation is needed before more detailed guidance on different formulations of desmopressin is made.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
			monosymptomatic nocturnal enuresis. De Bruyne, Pauline; De Guchtenaere, Ann; Van Herzeele, Charlotte; Raes, Ann; Dehoorne, Jo; Hoebeke, Piet; Van Laecke, Erik; Vande Walle, Johan. Journal of Pediatrics 173.2 (Feb 2014): 223-8.	
Ferring Pharmaceuticals	Disagree	Usage of both alarms and desmopressin	CDG/Clinical perspective: As highlighted within the CDG/clinical perspective and consideration of impact: 1) the guidelines are currently being misinterpreted with regard to recommendations for first-line interventions 2) alarms and desmopressin will be suited to different patients depending on their circumstances. The majority of healthcare professionals who do not specialise in enuresis are likely to interpret the treatment recommendations as “ALL children should be first tried on an alarm first and only if that fails should	Thank you for your comment. We are sorry that this guideline has been misinterpreted. However, CG111 clearly states: Consider whether or not it is appropriate to offer alarm or drug treatment, depending on the age of the child or young person, the frequency of bedwetting and the motivation and needs of the child or young person and their family (1.4.5). The guideline also states in recommendation 1.8.1 that alarms should be first line treatment in those whose bedwetting has not responded to advice on fluids, toileting or an appropriate rewards system unless they are considered undesirable by the child, young person or parent/ carer or are considered inappropriate.

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			they initiate medication in the form of desmopressin", in some cases this may be appropriate, although in other cases certain patient groups may not receive the treatment option most suited to them and their families. This will be exacerbated by the 'top line' heading within the guideline summary, which states the following: 'Offer an alarm as the first-line treatment to children and young people whose bedwetting has not responded to advice on fluids, toileting or an appropriate reward system' Many children and families, who are unsuitable for alarms, would be prescribed alarms first-line; even when compliance and adherence will be a significant issue. As a result desired outcomes may be delayed, failure rates increased, quality of life impacted and further unnecessary consultations and	In particular where bedwetting is infrequent, the parents/carers are having emotional difficulty coping with the burden of bedwetting or where the parents/carers are expressing anger, negativity or blame towards the child or young person. At present, we do not believe that the wording of these recommendations needs clarification. However, for interpretation of the guideline, 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.

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			management strategies adopted along with associated increased expenditure. The NICE CG111 should be aligned to the September 2014 quality standards which states that “The choice of initial treatment should be informed by the initial assessment, and should take into account the preference of the patient and their parents or carers. Factors such as age, associated functional difficulties and disabilities, financial burdens and living situations may affect their preferences”. As such the guidelines should unambiguously recommend both alarms or desmopressin first-line, the choice of which should be based on the circumstances and needs of the patient and their family.	
Disagree		Clinical effectiveness of desmopressin	As the GDG has indicated, “the new evidence relating to comparative evidence of demopressin melt and tablet formulations suggests that the melt formulation improves the	

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			probability of being a responder and improves compliance compared to the tablet formulation". We agree with the findings of the GCD and believe that Desmopressin melt demonstrates improved clinical outcomes. This is particularly the case for those aged between 5-8 years of age, which is supported by additional publications that have not been included within the current evidence summary. Bioequivalence of different formulations is an important measurement/consideration, and which can be influenced by drug-food interactions within this patient cohort. With many children's dinner times being 2-3 hours before they go to bed, it is important that the bioavailability of desmopressin remains as high as possible. It is known that the melt formulation has a more predictable bioavailability when	Of the references provided, two were not identified through the surveillance review because they were published before the literature search period (28/12/12 to 26/8/14) (Osterberg, De Guchtenaere) and one was not identified in the literature search (De Bruyne). However, assessment of the abstracts of these studies suggested that they were not RCTs or systematic reviews. As such, we cannot consider them as part of our surveillance review. The remaining study (Lottman et al.) was included in the original guideline. However, the GDG noted that the study was designed to assess the impact of patient choice and was not designed to evaluate the difference in effectiveness of the two formulations. With regards to desmopressin melt versus tablet, the evidence we identified during this surveillance review was limited since only one post-hoc analysis was identified. Further research investigating the efficacy of

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			compared to tablets1-3 and that the bioavailability of melt formulation is approximately 60% greater than that observed for the tablet formulation, allowing administration of lower dosages to achieve the same plasma concentrations.2,3 Recently, De Bruyne et al (European Journal of Paediatrics, 2014) demonstrated that the pharmacokinetic characteristics are far more predictable in the melt formulation compared to those for tablet. Even with the lower dose of the melt formulation (120ug), the same plasma concentrations are achieved as those of the tablet (200ug) formulation.4 This has also been highlighted in the study by de Guchtenaere et al (Journal of Urology, 2011), which concluded; "With meal combination desmopressin melt formulation has a superior pharmacodynamic profile to tablet, making it more suitable for the younger age group with a limited interval	melt versus tablet formulation is needed before more detailed guidance can be considered.

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			between meal and drug administration."1 As such, a shorter time to reach maximal effect and the sustained predictable antidiuretic duration of action (4-8 hours) should be a significant consideration in medication choice, especially in younger patients. The melt formulation also reduces the water intake required for administration which will improve response rates1,2. De Guchtenaere et al (2011) suggested that the melt formulation of desmopressin could result in 72ml less urine during their studied interval (overnight) and it was proposed that the production of "2.5 ounces less urine might mean the difference between waking up wet or dry".1 Furthermore, in a study conducted by H. Lottman et al, patients reported taking water with 13.1% of melt doses, compared with 76.9% of tablet doses2. The above as led us to believe that	

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			GC111 could do more to help physicians understand the implications for choice of desmopressin melt or tablet formulations and as such, offer guidance on when each should be considered. Bibliography: 1. De Guchtenaere A et al. Oral lyphylizate formulation of desmopressin: superior pharmacodynamics compared to tablet due to low food concentration. J Urol 2011;185(6):2308-13 2. Lottman H et al. A randomised comparison of oral desmopressin lyophilisate (MELT) and tablet formulations in children and adolescents with primary nocturnal enuresis. Int J Clin Pract 2007;61(9):1454-60 3. Østerberg O, Balchen T, Riis A, Senderovitz T. Pharmacokinetics of desmopressin in children and adults using a new oral lyophilisate. Arch Dis Child 2006;91:A31–4	

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
			4. De Bruyne et al.Pharmacokinetics of desmopressin administered as tablet and oral lyophilisate formulation in children with monosymptomatic nocturnal enuresis. Eur J Ped 2014;173(2):223-8	
The Paediatric Continence Forum	Disagree	Usage of both alarms and desmopressin	The PCF believes that there is a possibility, as this guideline is currently written, that healthcare professionals who do not specialise in enuresis could interpret the treatment recommendations to state that alarms should be offered as a first-line intervention ahead of desmopressin. In practical terms, this may result in children and families being issued with alarms as first-line treatment, despite the possibility of unsuitability. As such, this may lead to delayed improvements in outcomes, greater failure rates and impacted quality of life. The clinical guideline should be updated to state that treatment options should be offered following an initial	Thank you for your comments and for highlighting references during this consultation. We are sorry that this guideline has been misinterpreted. However, the guideline clearly states in recommendation 1.8.1 that alarms should be first line treatment in those whose bedwetting has not responded to advice on fluids, toileting or an appropriate rewards system unless they are considered undesirable by the child, young person or parent/ carer or are considered inappropriate. In particular where bedwetting is infrequent, the parents/carers are having emotional difficulty coping with the burden of bedwetting or where the parents/carers are expressing anger, negativity or

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
			assessment which takes into account the preferences of the patient and their parent/carer, including factors such as age, functional difficulties, and financial/living situations. The guideline should recommend either/both alarms and/or desmopressin as first-line treatments, the choice of which should be based on the needs of the patient and their family.	blame towards the child or young person. At present, we do not believe that the wording of these recommendations needs clarification. However, for interpretation of the guideline, 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.
		Clinical effectiveness of desmopressin	The PCF welcomes the GDG's recognition of the effectiveness of desmopressin, but believes that adequate evidence is available to provide guidance to clinicians on its different formulations – melt, tablet formulations and so on. Below is a summary of additional publications that have not been included within the evidence summary outlined in the surveillance review document.	Of the references provided, two were not identified through the surveillance review because they were published before the literature search period (28/12/12 to 26/8/14) (Osterberg, De Guchtenaere) and one was not identified in the literature search (De Bruyne) . However, assessment of the abstracts of these studies suggested that they were not RCTs or systematic reviews. As such, we cannot consider them as part of our surveillance review. The remaining study (Lottman et al.)

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
			Bioequivalence and bioavailability De Guchtenaere et al (Journal of Urology, 2011), Lottman et al (International Journal of Clinical Practice), and Østerberg et al (Journal of Clinical Pharmacology) note that melt formulation has more predictable bioavailability when compared to tablets, with the first two sources noting that the bioavailability of melt formulation is approximately 60% greater than that observed for tablet formulations. This allows for lower dosages to achieve the same plasma concentrations. Bioavailability is an important consideration as many children's dinner times occur 2-3 hours before they go to bed, and it is necessary to ensure that desmopressin remains as high as possible. Pharmacokinetic characteristics	was included in the original guideline. However, the GDG noted that the study was designed to assess the impact of patient choice and was not designed to evaluate the difference in effectiveness of the two formulations. With regards to desmopressin melt versus tablet, the evidence we identified during this surveillance review was limited since only one post-hoc analysis was identified. Further research investigating the efficacy of melt versus tablet formulation is needed before more detailed guidance can be considered.

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			A recent publication by De Bruyne et al (European Journal of Paediatrics, 2014) showed more predictable pharmokinetic characteristics in melt formulation in comparison to those for tablet. For example, a lower dosage of melt formulation (120ug) achieves the same plasma concentrations as those of the table formulation (200ug). Guchtenaere et al (Journal of Urology, 2011) also found that: “With meal combination desmopressin melt formulation has a superior pharmacodynamic profile to tablet, making it more suitable for the younger age group with a limited interval between meal and drug administration.” A shorter time to reach maximal effect and the sustained predictable antidiuretic action (between 4 and 8 hours) should warrant consideration in medical choice, especially for young children. Reduced water intake	

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			Guchtenaere et al (Journal of Urology, 2011) suggested that desmopressin could result in 72ml less urine during their studied interval (overnight), and it was proposed that the production of "2.5 ounces less urine might mean the difference between waking up wet or dry". This is supported by a study by Lottman et al (International Journal of Clinical Practice, 2007) reported taking water with 13.1% of melt doses, compared with 76.9% of tablet doses. Bibliography De Guchtenaere A et al. J Urol 2011;185(6):2308-13 Lottman H et al. Int J Clin Pract 2007;61(9):1454-60 Østerberg O, Balchen T, Riis A, Senderovitz T. Pharmacokinetics of desmopressin in children and adults using a new oral lyophilisate. Arch Dis Child 2006;91:A31–4	

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
			De Bruyne, Pauline; De Guchtenaere, Ann; Van Herzeele, Charlotte; Raes, Ann; Dehoorne, Jo; Hoebeke, Piet; Van Laecke, Erik; Vande Walle, Johan. Pharmacokinetics of desmopressin administered as tablet and oral lyophilisate formulation in children with monosymptomatic nocturnal enuresis. Journal of Pediatrics 173.2 (Feb 2014): 223-8.	
The Royal College of Nursing	Agree		We recommend that the guideline should be updated as we feel it remains misleading regarding first line treatments - although NICE clearly acknowledges that both desmopressin and the alarm are equally effective as first line treatment unless the guideline is read in full and algorithms reviewed the initial advice appears to indicate that alarms should be used first. There is also some emerging evidence that Desmomelt should be the preferred formulation of desmopressin as it has been shown to be more effective than	Thank you for your comments and for highlighting a reference during this consultation. We are sorry that this guideline has been misinterpreted. However, CG111 clearly states: Consider whether or not it is appropriate to offer alarm or drug treatment, depending on the age of the child or young person, the frequency of bedwetting and the motivation and needs of the child or young person and their family (1.4.5). The guideline also states in recommendation 1.8.1 that alarms should be first line treatment in

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
			the tablet and does not require a drink to administer Vande Walle J et al (2012) Practical consensus guidelines for the management of enuresis. Eur J Pediatr 171:971-983	those whose bedwetting has not responded to advice on fluids, toileting or an appropriate rewards system unless they are considered undesirable by the child, young person or parent/ carer or are considered inappropriate. In particular where bedwetting is infrequent, the parents/carers are having emotional difficulty coping with the burden of bedwetting or where the parents/carers are expressing anger, negativity or blame towards the child or young person. At present, we do not believe that the wording of these recommendations needs clarification. However, for interpretation of the guideline, 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. With regards to the highlighted reference, the study was not identified in the literature search for this surveillance review. Assessment of the abstract shows this to be a guideline on

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why Please insert each new comment in a new row	Response
				the management of enuresis. Unfortunately, as this study is not an RCT or systematic review, we are unable to consider it as part of our surveillance review. With regards to desmopressin melt versus tablet, the evidence we identified during this surveillance review was limited since only one post-hoc analysis was identified. Further research investigating the efficacy of melt versus tablet formulation is needed before more detailed guidance can be considered.

Appendix 2 Decision matrix

The table below provides summaries of the evidence for key questions for which studies were identified.

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
111-01: What is the family impact of children and young people aged under 19 who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-02: In children and young people with bedwetting, how does patient or parent/carer choice over treatment intervention influence treatment outcomes?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-03: What are the core elements of initial clinical history and examinations, and what are the core laboratory urine/ blood tests in the evaluation of children and young people under 19 years old who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-04: 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?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-05: 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?			
None identified.	None identified.	A GDG member highlighted that there have been a number of studies on the	The clinical feedback will not currently impact on CG111. This is because no study details were provided.

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
		value of investigations such as bladder ultrasound which suggest their usefulness. However, no details of these studies were provided.	
111-06: How should a psychological assessment be conducted, in the evaluation of children and young people under 19 years old who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-07: 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?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-08: What is the clinical and cost effectiveness of fluid and/or diet restriction for children and young people under 19 years who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-09: What is the clinical and cost effectiveness of lifting and waking for children and young people under 19 years who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-10: 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?			
None identified	**Simple Behavioural Interventions**	None identified through the GDG questionnaire.	The new evidence for simple behavioural interventions suggests

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		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 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

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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.		trials are needed.
111-11: What is the clinical and cost effectiveness of the use of star charts for children and young people under 19 years who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-12: What is the clinical and cost effectiveness of dry bed training for children and young people under 19 years who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-13: What is the clinical and cost effectiveness of enuresis alarms for children and young people under 19 years old who have bedwetting?			
<u>Evidence Update 2012</u> A UK based multicentre RCT[3] was identified that compared	An RCT[4] was identified that investigated the efficacy of enuresis alarm, desmopressin and a combination for the	Two GDG members highlighted the increasing availability of enuresis alarms and indicated that cheaper	The Evidence Update concluded that treatment with desmopressin or alarm is equally effective in reducing the number of wet nights. Furthermore,

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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 the two groups at the end of treatment.	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.	alarms are now available. Clinical feedback suggests that the 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.	the new evidence identified during this surveillance review suggests that enuresis alarms, desmopressin and a combination are all efficacious in treating nocturnal enuresis. 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

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
			suggests that whilst combination therapies are beneficial in the short term, over the long term the effect of alarms is better. The clinical feedback is unlikely to impact on guideline recommendations as no new evidence on the cost of alarms was identified through this surveillance review.
111-14: What is the clinical and cost effectiveness of desmopressin for children and young people under 19 years who have bedwetting?			
None identified.	**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,	None identified through the 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

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		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

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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 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		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 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.

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	exercises		
111-15: What is the clinical and cost effectiveness of anticholinergic medication for children and young people under 19 years who have nocturnal enuresis?			
<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.	None identified.	None identified through the 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.
111-16: What is the clinical and cost effectiveness of tricyclic medication for children and young people under 19 years who have bedwetting?			
None identified.	An RCT[9] examined the efficacy of nortriptyline for treating	None identified through the GDG questionnaire.	For children with ADHD, the new evidence suggested that nortriptyline

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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.		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

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
			considering an update of the guideline recommendations.
111-17: What is the clinical and cost effectiveness of dose escalation for children and young people under 19 years who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-18: 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?			
<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 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	None identified.	None identified through the 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 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

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
two groups and no significant difference in the rate of successful responses between the alarm and desmopressin groups.			new evidence in this area was identified through the 4 year surveillance review. Further research is need in this area before consideration for inclusion in the guideline.
111-19: What is the clinical and cost effectiveness of treating relapses in children after previously successful treatment for bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-20: What is the clinical and cost effectiveness of psychological interventions for children and young people under 19 years who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-21: What is the clinical and cost effectiveness of information and educational interventions for children and young people under 19 years who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-22: What is the clinical and cost effectiveness of alternative treatments for children and young people under 19 years who have bedwetting?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
111-23: In children under 5 years old with nocturnal enuresis, are there any preventive, prediction or treatment options which should be considered?			
Evidence Update (2012)	None identified.	A GDG member thought that	The Evidence Update suggested that

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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 frequently reported		there should be more clarity within the guideline on the age that a child can be expected to receive treatment for nocturnal enuresis.	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.

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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.			
111-24: 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?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
Research Recommendation: What elements of multicomponent 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?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
Research Recommendation: What is the clinical and cost effectiveness of standard interventions, for example alarm and desmopressin, for treating bedwetting in children and young people under 19 years old?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
Research Recommendation: What is the impact of bedwetting upon the psychological functioning and quality of life of children and young people and their families? How do these change with treatment?			
None identified.	None identified.	None identified through the	No relevant evidence identified.

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
		GDG questionnaire.	
Research Recommendation: 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?			
<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]	None identified.	None identified through the 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 could 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.

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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 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			

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
frequency, enuresis frequency or nocturnal urine production.			
Research recommendation: What is the prevalence of wetting and/or soiling in adolescence and what are the long-term consequences for adolescents with these problems?			
None identified.	None identified.	None identified through the GDG questionnaire.	No relevant evidence identified.
Areas not currently covered in the guideline			
Other Treatments for Nocturnal Enuresis			
None identified.	**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. **Electrical Nerve Stimulation**	None identified through the 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

Conclusions of previous reviews	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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.		study, more studies are needed so that firm conclusions about the usefulness of these interventions can be drawn.

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