A randomised controlled trial of a code-word enuresis alarm

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What is known about this topic:

- Enuresis alarm therapy is first-line treatment for bedwetting.
- Alarm failure is often linked to failure to wake to the alarm signal.

What this study adds:

- Rewarding recall of a personalised code word announced at the time of wetting can improve the arousal response and promote waking during alarm training.
- Rewarding arousal rather than rewarding dry nights may result in greater reduction in wet nights with alarm training.
- The code word alarm was found to be more effective than the control alarm in the children with monosymptomatic enuresis.

ABSTRACT

Objective: To compare a novel code-word alarm with a commercially available wireless alarm for treating enuresis

Design: Randomised controlled trial with blinding of study personnel and outcome assessors

Setting: A tertiary paediatric centre

Patients: Children aged six to eighteen with at least three wet nights per week in the previous 6 months referred by doctors

Outcomes: Primary outcome: the proportion who achieved a full response (14 consecutive dry nights) by 16 weeks. Secondary outcomes: change in frequency of wetting, duration of alarm training, percentage of wet nights that the child woke to the alarm, adherence to treatment, adverse events and satisfaction with treatment.

Results: Of the 353 participants, 176 were assigned to the code-word alarm and 177 to control. At 16 weeks, 54% (95% CI, 47% to 61%) in the experimental group and 47% (95% CI, 40% to 55%) in the control group had achieved a full response (p=0.22), with 74% and 66% respectively attaining a 50% or more reduction in wetting frequency (p=0.14). The experimental group woke more often than the control group (median percentage of waking 88% versus 77%, p=0.003) and had greater reduction in wet nights (median reduction 10 versus 9 nights per fortnight). Fewer in the experimental group discontinued therapy before achieving a full response (27% versus 37% discontinued, p=0.04). There were no significant differences in relapse rates at 6 months, adverse events or satisfaction between the two alarms. In a post hoc subgroup analysis of children with monosymptomatic enuresis, more in the experimental group achieved a full response (66% versus 52%, p=0.047), with higher median percentage of waking (89% versus 79%, p=0.006) and greater reduction in wet nights (median reduction 12 versus 9 nights per fortnight).

Conclusions: Although the code-word alarm increased waking, no difference in full response rates was demonstrated between the two alarms.

INTRODUCTION

Enuresis affects up to 20% of children[1] and impacts on sleep, self-esteem and quality of life, which can be reversed with successful treatment[2-4]. In enuresis, the normal arousal response to bladder distension is defective during sleep, with polysomnographic changes from deep to light sleep occurring without conscious awakening in many[5,6]. Alarm therapy, the first line treatment for enuresis[7], conditions the child to wake to an auditory stimuli with wetting and either void in the toilet or inhibit voiding by contracting their urethral sphincter[8], eventually learning to wake in response to bladder distension during sleep. Although this simple therapy is often effective, failure is common (25-35%)[7], and thought to be due to failure to wake to the alarm or poor adherence to treatment.

Although high sleep arousal thresholds is thought to be the reason why children fail to wake to the alarm, poor motivation to wake may also be a contributing factor. Motivation has been shown to enhance arousal to auditory stimuli during sleep in adults [9]. We hypothesized that by producing a higher level of arousal during alarm training, the arousal response to bladder distension during sleep would improve resulting in better treatment outcomes. We designed an enuresis alarm that promotes waking by encouraging recall of a personalised code word and compared this with a commercially available enuresis alarm.

METHODS

Participants: Children aged six to 18 years with enuresis at least three nights per week in the preceding six months, who were referred by their family doctor or paediatrician to the study for alarm therapy were invited to participate. Children with monosymptomatic enuresis (night wetting only), non-monosymptomatic enuresis (night wetting with lower urinary tract symptoms) and those who had previously failed alarm training were included. Children with enuresis secondary to neurological or urological problems were excluded.

Before enrolment, potential participants completed a 14-day bladder diary to determine eligibility and baseline measurements, and a questionnaire to identify demographic details, severity of wetting, type of enuresis (monosymptomatic or non-monosymptomatic) and previous treatments received.

Study design: Participants were randomly assigned to either the code-word alarm or a commercially available wireless enuresis alarm. Treatment ceased after 16 weeks of alarm training or when the child achieved 14 consecutive dry nights (whichever came first), as recommended by the National Institute for Health and Care Excellence (NICE) Guidelines[10]. The randomisation sequence was computer generated and stratified according to gender and age by the method of minimization, and performed by an independent randomization service. Allocation occurred via a telephone call to the service, with investigators, clinicians and data analysts unaware of group assignment. Families were aware of their assigned alarm but were unaware which was the 'novel' arm because the control alarm was not commercially available in Australia at the time of the study and therefore both alarms looked unfamiliar.

Interventions: The code-word alarm delivered a pre-recorded personalised code word when the child wet at night. Children were encouraged to remember the code word the next morning. We instructed the parents to reward recall, but did not specify what the reward should be. We hypothesised that a higher level of arousal is required for remembering and recalling a code word than from waking to the sound of the alarm, the standard method for arousal.

The code-word alarm comprised of a wireless wetness sensor (secured in a pad worn inside the child's underpants) and an alarm box (containing a digital voice recorder for parents to record personalised code words for their child) located beside the child's bed. When wetting occurred, moisture was detected by the sensor and the alarm sounded. When the child woke

and deactivated the alarm, the pre-recorded code word was announced and the child was encouraged by their parents to wake and void in the toilet. This code word changed daily. The control alarm was a wireless alarm that was commercially available in the United Kingdom at the time of the study (http://www.malemmedical.com/wireless-alarm-record-wetness-sensor-and-toilet-trainer). The attachment of the sensor and location of the alarm box was similar to the experimental group. When wetting occurred, the alarm sounded with an identical noise to the code-word alarm, and the child was encouraged by their parents to wake and void in the toilet. However, there was no pre-recorded code word with the control alarm. To ensure the treatments received by both groups were as similar as possible, instructional DVDs with identical wording (apart from the instructions for setting the code word for the experimental alarm) were provided to families.

Outcomes: Standardised outcomes were reported using the 2006 International Children's Continence Society (ICCS) definitions [11]. We compared frequency of wetting over 14 days at baseline with the end of treatment. In the original 2006 ICCS definition, a "full response" was defined as 14 consecutive dry nights (or completely dry), "response" as 90% to 99% reduction in enuresis compared with baseline, "partial response" as 50 to 89% reduction and "nonresponse" as 0 to 49% reduction. We added a "worse" category for those whose wetting increased. Relapse was defined as more than one wet night per month after achieving full response and continued success was no relapse within 6 months of ceasing treatment.

The ICCS definitions changed in 2014[12] and we have also reported outcomes using these updated definitions as a sensitivity analysis. In the 2014 definitions, the term "full response" was changed to "complete response", "partial response" was redefined as 50 to 99% reduction and "non-response" was less than 50% reduction in wetting compared with baseline.

The primary outcome was the proportion of children who achieved full response (14 consecutive dry nights) in the experimental and control groups by 16 weeks. Secondary outcomes were change in frequency of wetting over 14 nights, achieving more than 50% reduction in wetting compared with baseline, duration of alarm training, percentage of wet nights that the child woke to the alarm, adherence to treatment, discontinuation of alarm therapy before achieving a full response, adverse events and satisfaction with treatment by parents and children. We chose waking to the alarm as an outcome of interest as we wanted to assess whether improved waking will result in improved treatment outcomes. Waking was determined by diary records of the child being able to recall the code word the next morning in the experimental group and the child speaking to the parents when the alarm sounded for controls. Adherence to alarm training was measured as the percentage of nights on treatment that the child wore the alarm. For those who chose to discontinue alarm training, the date they discontinued treatment was used as their end of treatment date. In those who achieved a full response, we also compared the time to achieve a full response and relapse within 6 months of ceasing alarm training. The relapse rate was used to assess the sustainability of the alarm training after cessation of treatment.

Follow up procedures: The study coordinator contacted participants bi-weekly during alarm training and bi-monthly after cessation of treatment for a total of 12 months from enrolment. Parents were requested to complete diaries recording treatment response and adherence to treatment during alarm training, and wet nights after cessation of treatment. Routine clinical care was provided after cessation of alarm training, including the use of medication or further alarm training as appropriate.

Statistical methods: We aimed to recruit 320 children (160 in each study group), assuming a full response rate of 65% in the control group (as reported in previous studies)[7], and 80% in

the code-word alarm group (based upon single arm pilot data). This number would provide an 80% power to detect a difference of at least 15%, with a two-sided type I error of 5% and assuming a non-adherence rate of 10%.

We used an intention-to-treat approach and included patients who discontinued alarm training before achieving a full response in the denominator. Descriptive results were presented as frequencies and percentages for categorical variables and as medians and interquartile range (IQR) for continuous variables. In our primary analysis, we compared the proportion of children who attained a full response by 16 weeks in the experimental and control groups. The response of those who discontinued alarm therapy before achieving a full response and those who continued to wet at 16 weeks were derived from their treatment diaries as coded at the time of alarm discontinuation. The chi-squared statistic was used to test for a difference between proportions and the Mann-Whitney test applied to continuous variables, due to the skewness of their distribution.

A follow-up relapse at 6 months was defined for a child if one or more bi-monthly contacts reported a relapse during that time period. If one or more bi-monthly contacts were missing, the relapse status at 6 months was based on the available contact information. We repeated the analysis on the subset of children who had complete information for all bi-monthly contacts as a sensitivity analysis and the results were similar. Although relapse at 12 months was an outcome initially planned in the protocol, the amount of missing data did not allow us to analyse it.

As most previously published data on alarm therapy for enuresis was conducted in children with monosymptomatic enuresis (bedwetting only) [7], we conducted a post-hoc subgroup analysis of these patients. This population is known to be more responsive to alarm therapy and the subgroup analysis enabled our study to be compared with other studies of alarm

therapy[7]. The subgroup analysis used the same methodology to compare primary and secondary outcomes across the trial arms. All reported p values were two-sided and the significance level was set at 0.05.

The study was approved by The Children's Hospital at Westmead Ethics Committee (Project Number 2007/063). Informed consent was obtained from participants and their parents. The study was funded by a National Health and Medical Research Council grant (Grant Number 570761). The study was registered with The Australian New Zealand Clinical Trials Registry: (ACTRN12609000070235) https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=83457. All alarms used in the trial were purchased or built by the research team.

RESULTS

The study was conducted at the Children's Hospital at Westmead, Sydney, Australia. Three hundred and fifty three children were enrolled in the study between May 2009 and December 2010, with 176 allocated to the code-word alarm and 177 to the control alarm (Figure 1). There were two (1.1%) children lost to follow up in each arm. Although we were able to obtain information about their response at 16 weeks, we were unable to obtain diary data on other outcomes (Figure 1).

Baseline characteristics were well matched, with the median age being 8.4 and 8.1 years, 62 and 60% being male, 88 and 90% with primary enuresis and 56 and 57% with monosymptomatic enuresis for the experimental and control groups, respectively. Many had tried treatments previously, including alarm training in 10% experimental and 12% controls, desmopressin in 22% of both and tricyclic antidepressants in 5% and 4% respectively (Table 1). As the treatment outcomes were similar between those with primary and secondary enuresis, we combined primary and secondary enuresis when reporting outcomes.

Table 1: Characteristics of participants

	Code word Alarm N=176 (%)	**Control Alarm** N=177 (%)
Age (years)		
6-7	75 (43)	83 (47)
8-9	55 (31)	47 (27)
10-12	33 (19)	33 (19)
13-18	13 (7)	14 (8)
Male	109 (62)	107 (60)
Primary enuresis	155 (88)	160 (90)
Monosymptomatic	98 (56)	101 (57)
Frequency of bedwetting *		
<1 per month	1 (1)	1 (1)
1-3 times per month	1 (1)	0
1-2 times per week	6 (3)	7 (4)
3-7 times per week	111 (63)	119 (67)
>once per night	55 (31)	50 (28)
Not sure	2 (1)	0
Severity of bedwetting		
Wet underpants	3 (2)	0
Wet pyjamas or nappies	121 (69)	125 (71)
Wet bed	52 (30)	52 (29)
Previous treatment		
Alarm	18 (10)	22 (12)
Desmopressin	39 (22)	39 (22)
Tricyclic antidepressants	8 (5)	7 (4)

* All participants had at least 3 wet nights per week documented on their baseline bladder diary. However this table reports the frequency of bedwetting in the preceding 6 months as recorded on the demographic questionnaire, which differed from their baseline bladder diary

Primary outcome:

54% (95%CI, 47% to 61%) in the experimental group and 47% (95%CI, 40% to 55%) controls (p=0.22) achieved 14 consecutive dry nights by 16 weeks (Table 2).

Secondary outcomes:

Improvements in bedwetting: 74% (130/176) experimental versus 66% (118/177) controls attained 50% or more reduction in bedwetting at the end of alarm training (p=0.14), with 2% versus 4% achieving a response (90%-99% decrease in wetting), 18% versus 15% a partial response (50-89% decrease in wetting), 24% versus 29% a nonresponse (0-49% decrease in wetting) and 2% versus 5% being worse. According to the 2014 ICCS definitions, 74% (130/176) in the experimental group versus 66% (118/177) controls had a complete or partial response, and 26% versus 34% respectively had a nonresponse (Table 2). The median reduction in wet nights was 10 versus 9 nights per fortnight in the experimental and control groups respectively (p=0.029) (Table 3).

Length of treatment: The median length of treatment was 54 days for the experimental group and 61 days for controls (p=0.72). The median time to achieve a full response (for those who became dry) was similar, with 46 versus 50 days respectively (p=0.98).

Arousal response: The median percentage of wet nights the child woke to the alarm was 88% in the experimental group and 77% for controls (p=0.003) (Table 3 and 4).

Adherence to alarm training: The percentage of nights during treatment that the child wore the alarm was similar between the two groups, with 91% experimental and 89% controls (p=0.32) (Table 3). Children who achieved a full response on average wore the alarm more consistently than those who did not achieve a full response (94% versus 86%, respectively, p<0.001).

Table 2: Trial outcomes

	Code word Alarm N=176 n (%)	**Control Alarm** N=177 n (%)	**p-value**†
Primary outcome			
Full response	95 (54)	84 (47)	0.22
*Other categories of response**			
Response (90-99%)	4 (2)	7 (4)	
Partial response (50-89%)	31 (18)	27 (15)	0.41
No response (0-49%)	42 (24)	51 (29)	
Worse (<0%)	4 (2)	8 (5)	

*Categories or response according to ICCS definitions[11] Based on change in wetting at the end of treatment compared to baseline
†Chi-square test comparing change in wetting from baseline between the two treatment groups.

Table 2b: Outcomes of the code word and control arms according to 2014 ICCS definitions[12]

	Code word Alarm N=176 n (%)	**Control Alarm** N=177 n (%)	**p-value**†
Primary outcome			
Complete response	95 (54)	84 (47)	0.22
*Other categories of response**			
Partial response (50-99%)	35 (20)	34 (19)	0.32
No response (<50%)	46 (26)	59 (34)	

*Categories or response according to the NEW ICCS definitions based on change in wetting at the end of treatment compared to baseline[12] †Chi-square test comparing change in wetting from baseline between the two treatment groups.

Table 3: Secondary outcomes by treatment groups

	All patients (N=353)			Monosymptomatic patients (N=199)		
	Code word Alarm N=176	**Control Alarm** N=177	**p-value**	**Code word Alarm** N=98	**Control Alarm** N=101	**p-value**
Secondary outcomes						
>50% improvement (%)	130 (74%)	118 (67%)	0.14†	78 (80%)	72 (71%)	0.17†
Reduction in wet nights, median (IQR)	10 (6-14)	9 (3-13)	0.029‡	12 (7-14)	9 (5-13)	0.010‡
Length of treatment in days, median (IQR)	54 (34-100)	61 (37-97)	0.72‡	50 (31-83)	56 (36-99)	0.096‡
Percentage of wet nights woke to alarm - median % (IQR)	88 (63-100%)	77(56-93%)	0.003‡	89 (64-100%)	79(54-94%)	0.006‡
Percentage of nights on treatment alarm worn - median % (IQR)	91 (34-100%)	89 (37- 97%)	0.32‡	94 (79-98%)	89 (72-98%)	0.27‡
Chose to stop (%)	48 (27%)	66(37%)	0.044†	22 (22%)	31 (31%)	0.19†
Any relapse in 6 months* (%)	62 (67%)	51 (62%)	0.50†	40 (63%)	38 (58%)	0.53†
Adverse reactions (%)	30 (17%)	39 (22%)	0.24†	2 (2%)	5 (5%)	0.45†
Time to achieve full response* - median (IQR)	46 (34-68)	50 (32-65)	0.98‡	44 (33-60)	45 (30-64)	0.97‡

IQR - Interquartile range; *Only for whose who achieved a full reponse; † Chi-square test; ‡ Mann-Whitney test

Table 4: Percentage of nights child woke to alarm by trial arm and response categories according to ICCS (International Children's Continence Society)[10] by trial arm

	Code word Alarm N=176 Median % of nights (IQR)	**Control Alarm** N=177 Median % of nights (IQR)	**p-value**†
*ICCS categories of response**			
Full response (100%)	93 (75-100)	82 (63-97)	0.003
Response (90-99%)	52 (30-72)	58 (38-75)	0.93
Partial response (50-89%)	82 (62-98)	71 (55-86)	0.22
No response (0-49%)	67 (41-88)	72 (31-93)	0.69
Worse (<0%)	76 (48-88)	31 (4-92)	0.41

IQR - interquartile range; *Based on percentage of improvement; † Mann-Whitney test

Attitude to alarm training: 48/176 (27%) in the experimental group and 66/177 (37%) controls chose to discontinue training within the 16 week treatment period before achieving 14 consecutive dry nights because they did not like training (p=0.044). Adverse effects were similar between groups (14% versus 16% respectively) (Table 3). The most commonly reported adverse effect was sleep disturbance (14 versus 17). Other reported adverse effects included the child being frightened by the alarm (2 versus 4) and alarm training triggering sleepwalking and nightmares (1 in each group). Overall, most children (90% versus 86%) and families (95% versus 93%) reported being happy with the treatment received.

Relapse: Relapse rates assessed at 6 months after cessation of alarm training were similar in the two arms, with 67% of those who had achieved a full response in the experimental group and 62% in the control group reporting relapse (p=0.50) (Table 3).

Subgroup analysis of children with monosymptomatic enuresis:

There were 199 children with monosymptomatic enuresis, with 98 allocated to the code-word alarm and 101 to the control alarm (Figure 1). Of those with

monosymptomatic enuresis, 66% (65/98) in the experimental group versus 52% (53/101) controls achieved full response by 16 weeks (p=0.047).

The median reduction in wet nights was greater in the code-word alarm group, with 12 nights reduction per fortnight versus 9 nights compared with baseline (p=0.01). The median percentage of wet nights the child woke to the alarm was also higher for the experimental group, with 89% versus 79% of wet nights waking (p=0.006). The median length of treatment and the relapse rates at 6 months were similar in the two arms (Table 3).

DISCUSSION

In our study the full response rate was not higher for the code-word alarm group than controls for the whole cohort, although there was a small but significant reduction in the median number of wet nights (10 versus 9 nights per fortnight) and increase in median percentage of wet nights the child woke to the alarm (88% versus 77%) favouring the code-word alarm. We propose that the inclusion of participants who had non-monosymptomatic enuresis (who may or may not have received treatments for their lower urinary tract symptoms), those who had previous failed treatment, as well as those who chose to stop alarm training before achieving a full response contributed to the lack of difference seen between the two groups. Children with non-monosymptomatic enuresis are more likely to have multiple episodes of wetting at night compared with the monosymptomatic group, which would make alarm training more difficult and may result in desensitisation to the alarm. We included these children in our study for ethical reasons because they represent a typical clinical population who commonly use alarm therapy.

This is the largest study of alarm therapy for treating enuresis, and one of the few head to head studies comparing a novel alarm with the best current treatment[7].

Interestingly Van Londen's paper demonstrated that immediately rewarding the child for correct behaviour at the time of waking was more effective than delayed rewards for dry nights the following day, and that both were better than receiving no reward[13]. In our study, we found that delayed reward for recall of the code word (which required increased arousal at the time of wetting) was better than delayed reward for dry nights, suggesting that rewarding correct behaviour is better than rewarding for a desired outcome. The cost of the two alarms used in our study is very similar.

Limitations of this study include that it was not powered to adequately address the large proportion of children with non-monosymptomatic enuresis[14], which was double the expected in the population, possibly due to the setting of a tertiary paediatric centre with more complex referrals[14]. Another limitation was our choice of a full response as the primary outcome which may have been too stringent, as clinically significant differences in other outcomes may have been missed.

The overrepresentation of children with non-monosymptomatic enuresis in our study is likely to bias our study towards the null. Hence, we conducted a post-hoc subgroup analysis of the monosymptomatic group, as most published studies of alarm therapy including the Cochrane systematic review[7] predominantly included children with monosymptomatic enuresis. Our post-hoc analysis found a significant difference in full response rate, median reduction in wet nights and median percentage of wet nights the child woke to the alarm suggesting that the code-word alarm is more effective than the control alarm in monosymptomatic enuresis. These results are consistent with what was found in the Cochrane review[7]. However, as this analysis was conducted post-hoc, these results should be interpreted with caution.

CONCLUSIONS

The findings from our study have implications for clinicians who treat children with nocturnal enuresis. The focus of alarm training has traditionally been on achieving night dryness. Encouraging parents to reward arousal (rather than rewarding dry nights) when their child is alarm training is relatively simple and is likely to be associated with a reduction in wet nights, although this may not necessarily lead to complete resolution of wetting.

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Potential conflict of interest: PC is one of the inventors of the code-word alarm. The Children's Hospital at Westmead has patented the code-word alarm which was tested in this study and is in the process of commercialising this alarm.

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Contributorship statement: All authors had no relationship with the NHMRC funder. The first author (PC) is an inventor for this device and the Children's Hospital at Westmead has funded the patent application and is currently in the process of commercialising this novel alarm.

PC conceptualised the project and is responsible for the design, conduct, analysis and write up, PS, MK and SH were involved in data collection, data analysis and write up, AT and PM were involved in the data analysis and write up and JC was involved in the design, analysis and write up of the study. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

References:

1. Bower WF, Moore KH, Shepherd RB et al. The epidemiology of childhood enuresis in Australia. *Br J Urol.* 1996;78(4):602-6.

2. Hagglof B, Andren O, Bergstrom E et al. Self-esteem before and after treatment in children with nocturnal enuresis and urinary incontinence. *Scan J Urol Nephrol Suppl.* 1997;183:79-82.

3. Theunis M, Van Hoecke E, Paesbrugge S et al. Self-image and performance in children with nocturnal enuresis. *Eur Urol.* 2002;41(6):660-7.

4. Ertan P, Yilmaz O, Caglayan M et al. Relationship of sleep quality and quality of life in children with monosymptomatic enuresis *Child Care Health Dev.* 2009;35(4):469-74.

5. Watanabe H, Azuma Y. A proposal for a classification system of enuresis based on overnight simultaneous monitoring of electroencephalography and cystometry. *Sleep.* 1989;12(3):257-64.

6. Kawauchi A, Imada N, Tanaka Y et al. Changes in the structure of sleep spindles and delta waves on electroencephalography in patients with nocturnal enuresis. *Br J Urol.* 1998;81 Suppl 3:72-5.

7. Glazener CMA, Evans JHC, Peto RE. Alarm interventions for nocturnal enuresis in children. *Cochrane Database of Systematic Reviews.* 2005(2):CD002911.

8. Mowrer OH, Mowrer WM. Enuresis—a method for its study and treatment. *Am J Orthopsychiatry.* 1938;8(3):436-59.

9. Zung WW, Wilson W. Response to auditory stimulation during sleep: discrimination and arousal as studied with electroencephalography. *Arch Gen Psychiatry.* 1961;4(6):548.

10. Nunes DV, O'Flynn N, Evans J et al. Management of enuresis in children and adolescents: summary of the NICE guideline. *British Medical Journal, 341*(2), c5399. doi: http://dx.doi.org/10.1136/bmj.c5399

11. Neveus T, von Gontard A, Hoebeke P et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. *J Urol.* 2006;176(1):314-24

12. Austin PF, Bauer SB, Bower W et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the Standardization Committee of the International Children's Continence Society. *J Urol.* 2014;191(6):1863-5.

13. Van Londen A, Van Londen-Barentsen MW, Van Son MJ,et al. Relapse rate and subsequent parental reaction after successful treatment of children suffering from nocturnal enuresis: a 212 year follow-up of bibliotherapy. *Behav Res Ther.* 1995;33(3):309-311.

14. Forsythe WI, Redmond A. Enuresis and spontaneous cure rate: study of 1129 patients. *Arch Dis Child.* 1974;49 259-63.