Scheduled Awakenings for the Treatment of Nocturnal Enuresis

Benjamin Whittam, M.D., M.S., Pediatric Urology

Riley Hospital for Children

705 Riley Hospital Dr., Suite 4230

Indianapolis, IN 46202

NCT Number: 1601620278

Sub-Investigators:
Shelly King, C.P.N.P., Pediatric Urology/ Riley Hospital for Children
Adam Rensing M.D., Depart of Urology
Konrad Szymanski, M.D., MPH., Pediatric Urology/Riley Hospital for Children
William Bennett, M.D., Pediatric and Adolescent Comparative Effectiveness Research

6.15.18

Table of Contents:

1.0 Background

Primary monosymptomatic nocturnal enuresis (PMNE) is defined by the Diagnostic & Statistical Manual of Mental Disorders (DSM- IV) as an involuntary voiding of urine during sleep, with a severity of at least twice a week, in children aged >5 years in the absence of congenital or acquired defects of the central nervous system(1-3). Other etiologies that cause bed wetting such as cardiopulmonary, neurologic, endocrine or urologic diseases should be ruled out (1). Secondary nocturnal enuresis is defined nocturnal enuresis after at least 6 month of continuous dryness without prior without intervention (1, 4).

PMNE affects 10-20% kids at 5 years old (1, 4, 5). It does resolve spontaneously so that 5% of 10 year olds and 1% of 15 year olds are still affected (2-4). Is more common in boys. While the disease its self is benign, and improves without intervention, it does pose a significant social and emotional burden on the child and their family. These include parental disapproval, sibling teasing, and inability to attend sleep overs with peers, all of which lead to families seeking treatment options (3, 4).

Current treatments start with conservative management. This includes appropriate fluid intake, scheduled toileting during the day, avoidance of bladder irritants and constipation (4, 5). If these fail to improve symptoms or families are looking for a more active form of treatment, first line therapy is either a bed wetting alarms or desmopressin (1, 4, 5).

Bed wetting alarms typically attach to the child's clothes and sound when the device gets wet with urine. The goal of these devices is to alert the child that he or she has started to urinate and to allow them to be woken up, then voluntarily complete the void in the bathroom (1, 3, 6). While these devices are effective, they take about 4 weeks of constant use to show significant improvement and require continued use for at least 3 months to gain durable results (2, 5, 6). Alarms also suffer from a high discontinuation rate, as high as 30% (2, 3, 6). Problems associate with disruption of other family members, difficulty using the devices, and the device failing to cure PMNE have all been cited by families and reasons they stopped using the device (3, 6).

Desmopressin works as a vasopressin analogue to decrease urine production at night (1, 2, 4). It is quicker to improve symptoms compared to alarms once the treatment is discontinued the recurrence of PMNE is significantly higher than alarm devices (2, 4, 6).

The Lully Sleep Guardian was initially developed for use in night terrors. The device works by programing a vibrating disk that is placed under the child's bed to alter sleep patterns and prevent the onset of sleep terrors. The child is not woken up for the treatment of sleep terrors. The device has also be shown to anecdotally improve users' nocturnal enuresis. There have been no reports of safety concerns or hazards with the device (7, 8).

2.0 Rationale and Specific Aims

Aim 1: Determine the effectiveness of scheduled awakenings, with the Lully Sleep Guardian, in patients with PMNE, at reducing the frequency of bed-wetting.

3.0 Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• **Benign nocturnal enuresis** • **Age: 5 – 17** • **Access to an Apple iPhone, IPad, or iPod Touch preferred. (Will have a limited number if ipods available for loan if needed)**	• **Diurnal Enuresis** • **Constipation** • **Neurogenic Bladder** • **Any serious underlying cardiopulmonary problems that require diuretics or antihypertensive medications to manage** • **Any bladder active medications** • **Age: < 5 years of age; > 17 years of age** • **Cerebral Palsy** • **Mental disorders, mood disorders, or autism-spectrum disorder** • **Epilepsy or seizure history** • **Restless leg syndrome** • **Use of benzodiazepine/clonidine**

4.0 Enrollment

Patient Identification, Recruitment, Eligibility Determination

Participants may be recruited from the pediatric urology clinic at Riley Hospital for Children. These patients may be established patients, new patients, or referrals to Pediatric Urology not yet seen in clinic. We will also accept potential participants who are not affiliated with the Pediatric Urology clinic but meet inclusion criteria and have interest. These possible participants include those who attend bedwetting seminars conducted by Pediatric Urology and those who respond to advertising in the community. Potential participants may be recruited from the community through the use of flyers, social media, and INResearch

The initial contact with potential participants may be in person, by phone, or by email. A research team member will provide an overview of the study and be available to answer any questions posed by the family and/or patient. If the family has ongoing interest, they will be asked to complete screening questions to determine if the child meets the eligibility criteria for this study. If a potential participant responds directly to the flyer, they have the option to answer eligibility questions before interaction with a study team member.

To confirm potential participant does not meet any of the exclusion criteria and is eligible, the parent and participant will be asked to together complete two screening questionnaires, the Lully Q &A and the Vancouver questionnaire . Questionnaire results will be reviewed by a study team member and eligibility will be determined.

Consent Procedures

If the candidate is eligible, the informed consent, the assent (if applicable) and the HIPAA authorization will be obtained to enroll the patient. Informed consent and authorization procedures may occur in person or via phone. In either circumstance, the research team member will obtain written signature of consent and authorization. For children 7 – 17 years old, we will obtain child assent in addition to parents informed consent. After consenting, the participant will be immediately assigned to a treatment arm.

Treatment Arms

This study will enroll a total of 40 patients, with 20 in each treatment arm.

The first 20 subjects enrolled are scheduled to complete the study phases (S1 and S2) in the following order: 6 weeks of behavioral modifications plus the Lully device, followed by 6 weeks of behavioral modifications only (without the device). Subsequently, the last 20 subjects enrolled will undergo the study phases in the reverse order: 6 weeks of behavioral modifications only, followed by 6 weeks of behavioral modifications plus use of the Lully device This crossover will increase the validity of findings, but also ensure ease and simplicity when following patients.

The Lully device will be labelled in accordance with FDA investigational labelling requirements.

.
.

5.0 Study Procedures

During the initial and therapeutic phases of this study, participants are asked to enter responses daily into a Lully Study app. When the parent sets up the app, they enter their study email address, which is in the format iuenuresis16XX@lullysleep.com. The app will send a prompt each morning. The questions the participant is prompted to answer are: Did your child have a bed wetting episode last night? What time was it?

In a free text box the family is asked to add additional information to describe how wet the child was using the following 1-5 scale: 1- wet underwear; 2-wet underwear and damp pajamas; 3-soaked underwear, pajamas; 4-soaked pajamas, damp mattress; 5- soaked mattress

Initial Phase to establish baseline(4 wks)

1. The family will complete a QOL survey, the KIDSCREEN 27 before starting the initial 4 week phase.
2. The family will receive further counseling on behavioral modifications. Handout available for reference in Notes and Attachments.

3. Family will be provided with Malem Enuresis alarm to be used daily during 2 weeks of baseline data collection
4. Family will be asked to complete the KIDSCREEN 27 and the Vancouver questionnaire before starting therapeutic phase

.

Therapeutic phase

1. Each participant will complete the study phases (S1 and S2) in the order determined by their assigned treatment arm
2. During the 6 weeks of scheduled awakening protocol using Lully Sleep Guardian: each night, a scheduled awakening will be performed with the Lully pod. This will be used to reliably produce a brief awakening by titrating the device to a minimal awakening stimulus during the first night of use. If the brief awakening cannot be produced using the Lully pod, the parent will gently awaken the child
3. The family will complete the KIDSCREEN 27 and the Vancouver questionnaire at the cross-over between the study phases (S1 and S2) and at the completion of their 2 study phase

Study Completion

Family will be asked to return any equipment loaned for the purposes of this study to the Pediatric Urology Clinic at Riley

Compensation

Patient and families will be compensated with $1 per day for each day they respond to the daily questions prompted by the app about their child's nocturnal enuresis are replied to and an additional $5 per round of QOL surveys (2 surveys per round). The total will be summed at the conclusion of the study and paid to the participant as an Amazon gift card.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Adverse events will be monitored by the PI and co-investigators. As the participants will be receiving clinical urology care and the interventions are minimal risk, physical adverse events related to the study are not expected. Each event will be handled individually. Adverse events or unanticipated problems involving risk to the participants or others will be reported according to IRB standard operating procedures. If the adverse event represents an unanticipated problem and requires changes to the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others, it will be reported to the IRB using the Prompt Reporting Form within five business days of the investigator becoming aware of the event. Unless determined to not represent an unanticipated problem by HSO staff or the IRB Chair or Chair's designee, the report will be reviewed at a convened IRB meeting for possible action. Any serious unanticipated adverse events will be reported within 24 hours of becoming aware of the event.

7.0 Study Withdrawal/Discontinuation

The principal investigator will terminate the involvement of a given participant in the research study if they request to stop participating. The criteria which would result in removal from the study are: participant request to withdraw from the study. The principal investigator reserves the right to withdraw a family from the study if they do not meet the study requirements. Should this occur, the family will be notified by a member of the study team and paid for the activities they completed.

8.0 Statistical Considerations

This study is a simple effectiveness trial to determine if the Lully Sleep Guardian has any effect on benign nocturnal enuresis. If an effect is shown, the research team will use this study to perform a power calculation and facilitate a comparative effectiveness trial comparing Lully Sleep Guardian to current standards of care.

9.0 Privacy/Confidentiality Issues

Research material obtained from living human subjects will include medical records, with medical information collected by the PI/Research Nurse during screening/study visits; and data collected from the questionnaires and interviews.

All paper records containing identifying information will be kept in locked files accessible only to study staff and unlocked only while a study staff member is physically present. All computer records will require password access; computer workstations will be locked whenever a staff person leaves his or her desk.

10.0 Follow-up and Record Retention

Timeframe

Activity	Y1 Quarter 1	Y1 Quarter 2	Y1 Quarter 3	Y1 Quarter 4
Study run-up and information to clinicians and schedulers				
Training on device				
Actively enroll patients				
Data Analysis and Dissemination				

Record Retention

The duration of record retention will be at least seven years after the study has ended. Should the parent/guardian or child decide to withdraw from study participation, the participant's name will be removed from the excel datasheet where it had been recorded and the records will be destroyed.

References:

1. National Clinical Guideline C. National Institute for Health and Clinical Excellence: Guidance. Nocturnal Enuresis: The Management of Bedwetting in Children and Young People. London: Royal College of Physicians (UK) National Clinical Guideline Centre.; 2010.
2. Ahmed AF, Amin MM, Ali MM, Shalaby EA. Efficacy of an enuresis alarm, desmopressin, and combination therapy in the treatment of saudi children with primary monosymptomatic nocturnal enuresis. Korean journal of urology. 2013;54(11):783-90.
3. Glazener CM, Evans JH, Peto RE. Alarm interventions for nocturnal enuresis in children. The Cochrane database of systematic reviews. 2005(2):Cd002911.
4. Bayne AP, Skoog SJ. Nocturnal enuresis: an approach to assessment and treatment. Pediatrics in review / American Academy of Pediatrics. 2014;35(8):327-34; quiz 35.
5. Monda JM, Husmann DA. Primary nocturnal enuresis: a comparison among observation, imipramine, desmopressin acetate and bed-wetting alarm systems. The Journal of urology. 1995;154(2 Pt 2):745-8.
6. Onol FF, Guzel R, Tahra A, Kaya C, Boylu U. Comparison of long-term efficacy of desmopressin lyophilisate and enuretic alarm for monosymptomatic enuresis and assessment of predictive factors for success: a randomized prospective trial. The Journal of urology. 2015;193(2):655-61.
7. Rink A. Lully Sleep Guardian. In: Heinsimer K, editor. IU Health2016.
8. Lully Sleep Guardian - Proven to Stop Night Terrors: Amazon; 2016 [cited 2015 2016]. Available from: http://www.amazon.com/Lully-Sleep-Guardian-Proven-Terrors/dp/B011LOUNCI/ref=sr_1_1?ie=UTF8&qid=1457660065&sr=8-1-spons&keywords=lully+sleep+guardian&psc=1#customerReviews.