Sleep Promotion to Improve Diabetes Management in Adolescents With T1D

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Sleep Promotion to Improve Diabetes Management in Adolescents with T1D Pilot Study

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1.0 Background

Type 1 diabetes (T1D) is one of the most common chronic health conditions in youth, with over 18,000 new cases diagnosed each year, and the prevalence is increasing. The recommended treatment regimen is complex and demanding, including frequent blood glucose monitoring, insulin administration (via injections or pump), careful tracking of diet and activity levels, and frequent insulin adjustments. Adherence to this regimen is linked with better glycemic control and reduces the risk for acute and long-term medical complications. However, this intensive level of self-care is difficult to maintain and can negatively impact quality of life in adolescents. Problems with adherence are reported by the majority of adolescents with T1D (up to 93%), and poor diabetes-specific quality of life has been shown to contribute to suboptimal glycemic control. Despite recent advances in technology (e.g., insulin pumps, continuous glucose monitoring), many adolescents continue to have suboptimal glycemic control; a recent national study found that only 17% of adolescents were meeting the American Diabetes Associations' recommended targets. Thus, novel interventions are needed to improve glycemic control, adherence, and quality of life in adolescents with T1D.

Sleep disturbances have recently gained attention as a potential risk factor for individuals with diabetes, but the associations between sleep and diabetes outcomes are complex and bidirectional - poor sleep contributes to problems with glycemic control, and diabetes-related distress and poor glycemic control are likely to cause sleep disruptions. In laboratory studies with adults with T1D, reduced sleep duration and sleep disturbances have been shown to increase evening cortisol and growth hormone levels (hormones counter-regulatory to insulin) and increased insulin resistance. Results from a national survey indicate that nearly 70% of adolescents in the general population obtain insufficient sleep (defined as <8 hours/night), and similar rates have been reported in adolescents with T1D. Nevertheless, sleep characteristics, such as total sleep time, sleep/wake times, or sleep quality, are not routinely addressed in standards of care for youth with T1D, and the role of sleep in self-management and adherence is not fully understood.

Adolescents with T1D are at high risk for poor adherence and suboptimal glycemic control. Sleep disturbances, such as poor quality and insufficient sleep, are a potentially modifiable risk factor for poor diabetes outcomes in adolescents with T1D. We propose to pilot test a sleep-promoting intervention tailored for this population. By improving sleep quality and/or increasing duration of sleep, we may improve outcomes in adolescents with T1D through both an indirect, behavioral pathway (i.e., adherence) and a direct, physiological pathway (i.e., glycemic control). The proposed research is innovative in its plan to target sleep promotion in adolescents with T1D as a way to improve diabetes management, glycemic control, and quality of life.

2.0 Rationale and Specific Aims

Working from a biopsychosocial and contextual model of sleep, which highlights the need to consider the social environment and psychosocial factors, we propose to intervene on the modifiable aspects of sleep disturbance in adolescents. We have

conducted interviews with adolescents and their caregivers to identify barriers, facilitators, and consequences of insufficient sleep for adolescents with T1D. The results of these interviews have informed the development of an intervention protocol that is tailored to the needs of this population. We propose to pilot test a behavioral sleep intervention for adolescents with type 1 diabetes. This low-cost, innovative intervention is designed to induce greater sleep duration and higher quality of sleep in adolescents (age 13-17) through tailored exercises in sleep hygiene education, cognitive restructuring, and relaxation.

The **specific aim** of this project is:
To evaluate the feasibility and preliminary efficacy of this novel intervention with a pilot randomized trial of adolescents with T1D. The primary outcomes will be sleep quality and glycemic control, and secondary outcomes include adherence and quality of life.

Hypothesis: Adolescents who receive the sleep-promoting intervention will demonstrate improved sleep quality and glycemic control, as well as fewer problems with adherence and quality of life, as compared to those who receive usual care.

3.0 Animal Studies and Previous Human Studies

Dr. Jaser and colleagues conducted qualitative interviews with 25 adolescents with type 1 diabetes and their caregivers, which identified several barriers and facilitators to achieving sufficient sleep (PMCID: PMC6460925). Results from this study informed the intervention tested in the pilot study.

4.0 Inclusion/Exclusion Criteria

List the criteria:

- adolescent age 13-17
- adolescent has been diagnosed with type 1 diabetes for at least 12 months
- adolescent reports insufficient sleep (<8 hours/night most school nights)
- adolescent does not have a diagnosed sleep disorder or other health problem that would interfere with sleep
- adolescent and parent able to speak and read English

5.0 Enrollment/Randomization

Participants will be enrolled at the Children's Diabetes Program at Vanderbilt (Vanderbilt University Medical Center, [redacted], Nashville, TN 3[redacted]). A trained research analyst (RA) will approach families (teen and parent) in the diabetes clinic. The teen and their parents will be described, in-depth, details regarding the format and procedures of the study and address any questions or concerns the participants may have in a private space. After consenting/assenting and completing all baseline questionnaire data, teens will be given instructions to wear an actigraph watch and complete a sleep diary for 7 nights.

When the sleep watch and diary are returned in the pre-paid envelope, the teen will be randomly assigned to the intervention condition (Sleep Coach) or usual care. Randomization will be stratified by the adolescents' treatment type (insulin pump vs.

injections) to remove the possibility of confounding by differences related to insulin regimen. Randomization will be determined by a computerized program created by the biostatistician on the project (Chris Slaughter).

6.0 Study Procedures

At baseline and 3 months, teens and parents will complete surveys consisting of measures are widely validated and have been used successfully by our research team in previous studies. Questionnaire data collection is timed to correspond with regularly scheduled clinic visits. The measures take about 30 minutes to complete.

In addition, teens will receive 7 days of automated text messages to collect data on sleep habits 6 weeks after randomization. Each day, they will receive a series of 4 text messages, asking them to confirm the date, report the time they fell asleep the night before, the time they woke up that morning, and rate the quality of their sleep.
All data will be collected using REDCap.

Clinical data (HbA1c values, blood glucose data) will be extracted from participants' medical charts.

Teen Measures:
Self-Care Inventory (SCI-C): assesses key elements of the treatment regimen for T1D: diet, exercise, blood glucose monitoring, insulin administration, and attending medical appointments. The wording applies to various insulin regimens (i.e., pump and injections). It has been shown to have good reliability and validity. The mean score will be used in data analyses.

Pediatric Quality of Life (PedsQL) diabetes-specific measure. The 28 items will be summed to create a total diabetes-related quality of life score. Scaled scores range from 0-100, and higher scores reflect better quality of life.

Patient Health Questionnaire (PHQ-9) will be used as a measure of current depressive symptoms. The PHQ consists of 9 items, and higher scores indicate higher current levels of depression, with a score of 11 or higher suggesting clinical levels of depression, with sensitivity of 89.5% and specificity of 77.5% for detecting major depression.

The Child Hypoglycemia Fear Survey (C-HFS) is a measure of worries and behaviors that stem from fear related to hypoglycemia. The C-HFS consists of 33 items and has been shown to have good reliability and validity in this population.

The Daytime and Nighttime Activity Modules consists of six questions regarding daytime and nighttime activities that can impact sleep.

Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD): an eight item measure of how likely an adolescent is to doze in various situations. This scale has been shown to have good reliability and validity in children and adolescents.

Morningness-Eveningness Questionnaire: a widely used, ten item questionnaire that assesses perceived alertness across times of day to determine circadian rhythms.

Pittsburgh Sleep Quality Index (PSQI): a widely used, 19-item questionnaire assessing sleep habits and disturbances. It has been shown to have good validity and reliability.

Problem Areas in Diabetes: Teen Version (PAID-T): assesses feelings of day-to-day burdens and hassle related to diabetes. It is comprised of 26 items and has been demonstrated to have good reliability and validity in teens.

Adolescents will wear the Phillips Actiwatch Spectrum Plus, a wrist-worn accelerometer, continuously for 7 days, and will be asked to press the event marker at "lights out" and "lights on" times to demarcate time in bed. Actigraph data will be scored with Phillips Spectrum Plus software. Descriptive statistics will be used to summarize each of the primary sleep variables (% wake after sleep onset, time in bed, sleep efficiency, sleep latency, duration) over the 7 day week interval, and these will be entered in the REDCap database.

Parent Measures:
Self-Care Inventory - Parent (SCI-P): assesses key elements of adherence to the treatment regimen for T1D: diet, exercise, blood glucose monitoring, insulin administration, and attending medical appointments. The wording applies to various insulin regimens (i.e., pump and injections). It has been shown to have good reliability and validity.

The Parent Hypoglycemia Fear Survey (P-HFS): a measure of parent worries and behaviors that stem from fear surround their child experiencing hypoglycemia. The P-HFS consists of 33 items, and has been shown to have good reliability and validity in this population.

Problem Areas in Diabetes: Parent Revised Version (PAID-PR): assesses feelings of day-to-day burden and hassle associated with their child's diabetes. It is comprised of 18 items and has been demonstrated to have good reliability and validity.

Nighttime Behaviors Module: a six item questionnaire covering habits surrounding parent's nocturnal caregiving.

WHO-5 Well-Being Index (WHO-5): a brief, five item questionnaire that measures subjective quality of life, with higher scores indicating better quality of life. It has been shown to exhibit good psychometric properties.

Satisfaction Survey – completed by teens and parents at 3 month follow-up

Interventions

Participants randomized to the Sleep Coach condition (n=20) will receive a binder of study materials. These materials will include educational information on healthy sleep habits and how to implement strategies to improve sleep. Over the course of the study, teens will participate in three phone sessions with a trained Master's level interventionist (who will be supervised by a licensed clinical psychologist). During these sessions, the interventionist will go over informational materials with the teen and walk them through exercises designed to help the teen prepare for and practice health sleep habits. The

phone calls will take place at a time that the teen has indicated are convenient to them. The first phone call will last approximately 30 minutes. The second call will last approximately 10-15 minutes and take place about one week after the initial phone session. The third call will last approximately 10-15 minutes and will take place about three weeks after the second call. Parents will not participate in phone calls but will be provided with materials designed to help them support their teen in implementing healthy sleep habits.

Teens assigned to the Usual Care group (n=20) will have access to regular diabetes care.

7.0 Risks

Data collection requires participants (teens and parents) to spend approximately 30 minutes at each collection (baseline, 3 months) completing surveys. Teens will also spend a few minutes completing sleep diaries for 7 nights at baseline and 3 months.

Teens in the sleep coach condition will engage in 3 intervention phone calls that will last 10-30 minutes This is not anticipated to be an undue burden for the participants.

The potential benefit of this study is to gain knowledge on how to improve sleep in adolescents with Type 1 Diabetes. The results from this study will inform providers and caregivers on how to most effectively motivate adolescents to improve their sleep habits, which may have positive effects on glycemic control and diabetes management. In sum, there are more compelling benefits than risks.

Several steps will be taken to protect the subjects against risk. First, participants will be informed that they are free to skip any questions that they feel uncomfortable answering and that they are free to withdraw from the study at any time without penalty. There are no potential legal or social risks to participants consenting to participate in this investigation.

Additionally, if teen participants indicate self-harm on the 9th item of the PHQ-9 questionnaire or score 11 or higher, RAs will administered the Self-Harm Assessment and will notify the PI and the social worker. The PI and/or the Social Worker will determine the steps that need to be taken to ensure safety of the participant. RAs will not be asked to determine the clinical significance of the harm. RAs will speak with parents describing the results of the assessments and provide the family with a list of resources.

All children will receive clinical care throughout the course of the study. All diabetes treatment decisions will be made by the diabetes treatment team. All patients have access to the treatment team 24 hours/day and 7 days per week. Participants will be informed that they may discontinue the study at any time or skip any questions they do not feel comfortable answering. There are no potential legal or social risks to participants consenting to participate in this investigation. Parents will be told to follow the diabetes clinic providers' guidance on any questions related to diabetes management.

The PI will ensure that the trial is conducted according to the approved protocol and will be responsible for carrying out the data safety monitoring plan, which includes:
- Review of study components for data completeness and accuracy as well as protocol compliance
- Evaluate adverse events (AEs, described below) for severity, relationship to the research and actions to be taken
- Promptly report all severe AEs and unanticipated problems to the data and safety officer, IRB, and NIH

KSP will complete human subjects training prior to any contact with participants and maintain annual training. KSP will also complete Good Clinical Practice training for social and behavioral research annually.

Data Safety and Monitoring

Randi Streisand, PhD, CDE will serve as the Safety Officer for the project. Dr. Streisand is a clinical health psychologist and certified diabetes educator working in a clinical research setting with roles in research, clinical service, and training.
She a Professor of Psychology & Behavioral Health and Pediatrics, and she serves as the Director for Psychology Research across Children's National Health System, as well as the Diabetes Team's Director for Psychosocial Research and Service. Her current work is funded by the NIH and focuses on managing type 1 diabetes in young children, and she has served as PI or Co-I for several interventions focused on stress reduction and/or adherence in families of children with chronic illness.

Safety reports will be sent bi-annually (every six months) to the Safety Officer and annually to NIDDK and the Vanderbilt University IRB. The PI will prepare data for interim analyses, which will be conducted every 6 months by the biostatistician. The Safety Officer will review the safety reports in an aggregate fashion, blinded to treatment groups.

Safety Reports will provide a study summary and identify any problems or issues and will include details on the status of the study and/or preliminary findings. In addition, any deviations from protocol will be noted. Each safety report will include the following:
A table indicating the expected vs. actual enrollment per month, including number of patients approached, ineligible, and refused.
A table of overall subject status, as well as detail on each participant's progress through the study. This table will include information on the number of active participants, the number of participants who have completed the study, participants who drop out (including reasons) of the study and those who are unable to be reached (lost to follow up).
An enrollment report, indicating the racial ethnic characteristics of the study sample
A table indicating the demographic and key baseline characteristics (including A1C, depression, and adherence) by group.
A table listing all adverse events, actions taken, and outcomes.

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

Any adverse events occurring during the course of this trial will be collected, documented and reported by the PI (Dr. Sarah Jaser), to the Safety Officer (Randi Streisand, PhD, CDE), along with reporting to the NIDDK and institutional review boards as required. Although not anticipated, if any event is identified that may have caused any type of harm to a participant, study accrual will be immediately halted until the study team and DSMB can review the event and determine if any study procedures need to be revised. Study accrual will only resume after review of study protocol has been completed and any recommended revisions made as suggested by the DSMB.

9.0 Study Withdrawal/Discontinuation

Study participants may contact the study team if they wish to withdraw.

10.0 Statistical Considerations

Power Analysis: Based on effect sizes from cognitive-behavioral interventions to treat insomnia showing medium to large effect sizes for total sleep time after 3 months (***d*** = .71), we would need a sample of 52 to have sufficient power to detect a treatment difference in sleep time. With a sample of 40, we will have power of .71 to detect a significant treatment difference. The small sample size of this pilot study does not provide the power to test the efficacy of the intervention. The focus of this study is to see initial evidence for an effect on the direct target – improvement in adolescents' sleep duration and quality – as well as feasibility of the trial. By collecting A1C data for 6 months, we will be able to determine if there is an impact on glycemic control.

Preliminary Analyses: Preliminary Analyses: We will conduct unadjusted tests of the association of demographic covariates including gender, race/ethnicity income, fear of hypoglycemia, and circadian preference with sleep habits. While we anticipate our randomized design will mitigate confounding, adjusting for covariates associated with the sleep outcomes will improve the precision of our estimate of the treatment effect. Actigraph data will be scored with Phillips Spectrum Plus software with guidance from Vanderbilt's Sleep Core. Objective actigraph data will be supplemented with sleep diaries to determine bedtime and wake time. Descriptive statistics will be used to summarize each of the primary sleep variables: sleep efficiency, sleep latency, and total sleep time (duration) over the 7-day interval.

Longitudinal models will be conducted using baseline and follow-up data to determine the preliminary effect of the intervention on the primary outcomes (sleep quality and glycemic control), as well as the secondary outcomes of adherence and quality of life. The longitudinal responses will be analyzed using generalized least squares to account for correlation arising from taking repeated observations on the same subject over time. We anticipate that two measurements made more closely in time will be more highly correlated than measurements made distant in time, and we anticipate some longitudinal measures could have negative correlations (e.g. poor sleep on one night leading to better sleep on the next night). To those ends, we will use an unstructured correlation for the primary analysis. The choice of unstructured will be compared to other correlation structures using AIC. Mean time-response profiles over time will be flexibly modeled using restricted cubic splines. Analyses will provide estimates of effect sizes, within-subject variances, and between-subject variances to be used in power analyses for a full scale trial.

Feasibility and Acceptability: To determine the feasibility of the intervention, we will examine recruitment and retention data. Our benchmark for retention is ≥ 85%. In addition, fidelity checks will be conducted by audiotaping 20% of the telephone sessions, which will be coded for content by an independent rater. We propose a feasibility benchmark of ≥90% fidelity. Logistic regression will be used to determine if baseline covariates can be used to predict retention or fidelity

To evaluate acceptability of the intervention, we will examine participation (attendance), adherence (completion of homework), and satisfaction ratings. We propose a feasibility benchmark of ≥ 80% attendance. We will also conduct exit interviews with adolescents, including those who did not complete the study, to find out what they liked and did not like about the intervention. Interviews will be transcribed and analyzed with a content analysis approach to identify themes across participants. By integrating input from participants, we plan to maximize engagement with and increase feasibility in a large-scale trial.

11.0 Privacy/Confidentiality Issues

Confidential participant data will be safeguarded by multiple password protection requirements, data encryption, and locked secure storage of paper documents.

Only Key Study Personnel (KSP) will have access to research information, and all KSP will complete training in Good Clinical Practice.

Participants will be identified with an ID number; names will not be included on any data outside of RedCAP. Only research staff who have completed IRB training and have been added as KSP have access to the study RedCAP. All identifying information will be destroyed at the earliest possible time following completion of the study. All data will be analyzed by groups, with no potential for individual patients to be identified. Any publications arising from the study will not contain personal information.
Digital files will be erased after completion of the study.

12.0 Follow-up and Record Retention

Duration of the study is anticipated to be 2 years. All data will be analyzed by groups, with no potential for individual patients to be identified. Any publications arising from the study will not contain personal information.

Research records will be maintained for at least three (3) years from the date the research is closed with the IRB. All Health Insurance Portability and Accountability Act (HIPAA) related documentation will be maintained for at least six (6) years from the date of the last use or disclosure of the Protected Health Information (PHI).