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Teens and opioids postsurgery (TOPS): protocol for a prospective observational study describing associations between sleep deficiency and opioid use following outpatient surgery in adolescents

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ABSTRACT

Introduction The opioid crisis is a significant burden on adolescent public health in the USA. Medical use of prescription opioids is a pathway via which adolescents transition to opioid misuse, opioid use disorder and overdose. More than half of all opioids prescribed to adolescents are for pain management following surgery. Yet, little is known about the critical period following surgery during which adolescents initiate opioid misuse or the modifiable mechanisms (such as sleep deficiency) contributing to this process. This prospective observational study will broaden our knowledge by examining associations between sleep deficiency and opioid use and misuse following surgery. We will also examine behavioural, psychological, family and social factors linking sleep deficiency with opioid use and misuse.

Methods and analysis Adolescents (10–19 years) undergoing outpatient orthopaedic surgery, along with one parent, will be recruited from two paediatric hospitals, for a sample of 400 dyads. Adolescents will be assessed at six timepoints. Before surgery, participants will undergo comprehensive multimodal sleep assessments (sleep surveys and actigraphy). Participants will also report on previous substance use, pain intensity and psychosocial, family and social factors. Adolescents will then be closely monitored over the first 14 days following surgery using ecological momentary assessment methods to capture real-time, naturalistic, daily data on sleep, opioid use, pain and psychological factors (including mood, affect and subjective response to opioid use). Opioid use (total number of doses and duration) will be measured with an innovative electronic medication monitoring device following surgery. Follow-up assessments at 3 months, 6 months, 12 months and 24 months will track the development of opioid misuse over time. Our primary outcomes include opioid use during the immediate 14 days following surgery and the presence of opioid misuse at 24 months after surgery. Multilevel mediation models will determine associations between predictor variables and acute postsurgical opioid use. We will apply modern machine learning algorithms to develop and validate models predicting adolescent prescription opioid misuse at 24 months from surgery.

Ethics and dissemination This study was approved by Advarra's Center for Institutional Review Board Intelligence (CIRBI) (Protocol 00072049), which serves as the single IRB of record for this multisite study.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prospective, multicentre study design provides stronger evidence for causality than could be obtained from cross-sectional and retrospective designs.
⇒ Use of electronic medication monitoring technology (eCap) accurately measures opioid use in near-real-time, minimising subjective reporting bias.
⇒ Use of ecological momentary assessment (EMA) methods tracks sleep, pain, psychological factors and opioid use in near-real-time and naturalistic environment postsurgery, allowing for dynamic modelling of these relationships over time.
⇒ Sample attrition is common to all longitudinal studies.
⇒ Poor compliance is an acknowledged limitation of EMA protocols.

INTRODUCTION

Prescription opioid use is of high public health significance during adolescence. The past two decades have seen a significant increase in problematic opioid use behaviours among adolescents, including persistent use such as repeated prescription refills following surgery[1] or trauma[2] and opioid misuse.[3 4] The National Survey on Drug Use and Health (NSDUH) estimates that in 2019, more than 550 000 adolescents 12–17 years of age engaged in prescription opioid misuse[5] and more than 90 000 adolescents reported

having opioid use disorder (OUD).[5] Opioids (particularly fentanyl) are involved in most adolescent overdose deaths,[6] and more than 90% of individuals using heroin initiate opioid use via a medical prescription.[7] Epidemiological data show that prescription opioid misuse follows a developmental trajectory characterised by early initiation during adolescence before peaking in early adulthood (thereafter declining),[8] demonstrating a critical need for prevention efforts focused during the teenage years to reduce initiation of opioid misuse and disrupt opioid use trajectories.

There are several pathways to opioid misuse, however, increasing attention is being paid to the risk of developing opioid misuse among the >500 000 adolescents who are prescribed an opioid for surgery in the USA each year.[9–13] Opioids provide effective pain control and are appropriately considered a cornerstone in the management of acute postoperative pain following sports injury surgery.[14] Indeed, poorly controlled pain following surgery is associated with a host of negative consequences, including reduced engagement in postsurgery rehabilitation, delayed functional recovery and an increased risk for chronic postsurgical pain.[15 16] However, it is now recognised that a significant portion (up to 15% within 6 months) of adolescents develop iatrogenic problematic opioid use behaviours such as persistent opioid use and opioid misuse following surgery.[1 9]

Risk factors associated with postsurgical opioid use and opioid misuse remain poorly described. Much of our knowledge about postsurgical opioid use comes from studies with indirect methods such as data analysed from administrative datasets and pharmacy refills.[1] These studies share several limitations, including a lack of granular detail on actual opioid consumption and important covariates such as acute pain intensity, behavioural, psychological, family and social predictors associated with problematic opioid use following surgery.[17] These factors are critical in understanding postsurgical opioid use in adolescents. Addressing this gap in knowledge will lead to better understanding and predicting postsurgical opioid use, thereby facilitating more targeted interventions (eg, sleep management and trauma care) and support (eg, closer monitoring and increased follow-up visits) for adolescents at risk.

Sleep deficiency and circadian disruptions are implicated in the initiation of prescription opioid misuse and OUD. Sleep deficiency, as defined by the National Institutes of Health (NIH), is a broad construct that includes sleep deprivation (not getting enough sleep), non-circadian sleep (sleeping wrong time of the day), impaired sleep architecture (not achieving all required types of sleep), sleep disorders (eg, sleep disordered breathing, insomnia) and poor sleep quality.[18] Sleep deficiency is common among individuals with OUD,[19–21] but temporal relationships between sleep deficiency and the OUD trajectory (from problematic medical use via opioid misuse to OUD and overdose) remain poorly described. Data from several large, cross-sectional, population-based studies, including the National Longitudinal Study of Adolescent to Adult Health, the Youth Risk Behavior Survey, and the Monitoring the Future Study, indicate that adolescent sleep deficiency is associated with increased prevalence of prescription opioid misuse behaviours.[22–25] However, this research is cross-sectional and has not yet been replicated in prospective, longitudinal studies.

Therefore, prospective intensive longitudinal studies that assess experiences of sleep deficiency and opioid use behaviours in real-time natural settings are urgently needed to address several critical questions that remain. Specific questions include: (1) whether findings from population-based samples can be replicated in clinical samples, (2) whether sleep deficiency serves as a risk factor for the initiation of problematic opioid use behaviours, (3) which aspects of sleep deficiency (sleep deprivation, non-circadian sleep, sleep-disordered breathing, sleep quality) are most strongly associated with problematic opioid use behaviours and (4) which behavioural mechanisms (including pain experience and psychological factors) link sleep deficiency to problematic opioid use behaviours.

STUDY OBJECTIVES

To address these research gaps, aim 1 of this study is to test the direct and mediation pathways of sleep deficiency and opioid use following sports injury surgery. We hypothesise that (1) greater presurgery sleep deficiency will be associated with higher opioid use following surgery, (2) in the immediate postoperative period, concurrent sleep deficiency will be associated with increased opioid use during the following day and (3) pain and psychological factors will mediate the relationship between sleep deficiency and opioid use over the first 14 days postsurgery. Aim 2 is to develop and validate a multivariable prediction model to identify adolescents at increased risk for prescription opioid misuse over the 24 months following surgery. We hypothesise that greater sleep deficiency during the first 12 months following surgery, greater opioid use following surgery, a history of substance use, higher pain and higher psychological distress following surgery will predict an increased risk for prescription opioid misuse at 24 months.

METHODS

Study design and setting

The study uses a prospective observational cohort design. Figure 1 presents an overview of assessment timepoints. This study design was chosen because it (1) allows data collection in near real-time as events occur, reducing the likelihood of recall bias and improving the accuracy of the information and (2) can establish a clear temporal relationship between sleep deficiency and onset of opioid use, which is crucial for making causal inferences. Data collection started in March 2024 and continues through March 2028. The study sample will include adolescents

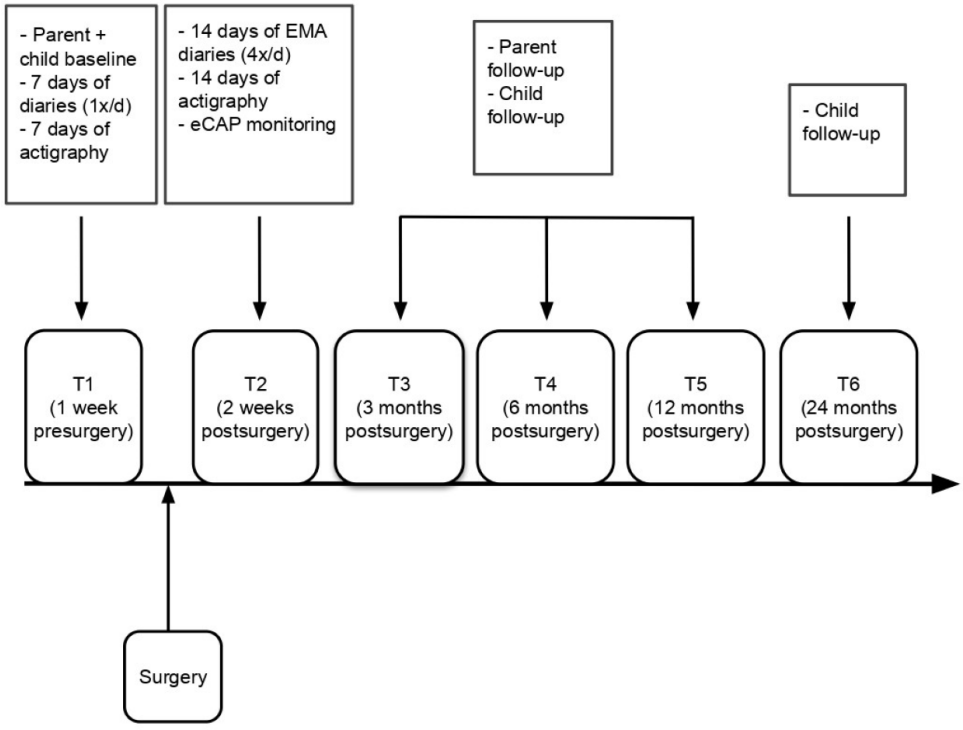

Figure 1 Overview of assessment timepoints. EMA: ecological momentary assessment.

10–19 years of age (and a parent) undergoing outpatient orthopaedic surgery with a target of 400 dyads. Eligible orthopaedic surgery indications include shoulder, elbow and knee surgeries associated with a sports-related injury. These surgeries were included as adolescents who are prescribed opioids following sports injury are at high risk for developing prescription opioid misuse.[26] National efforts have focused on reducing or eliminating opioid prescribing for less invasive surgical procedures in adolescents. However, the surgical procedures captured in this proposal are sufficiently extensive that >90% of adolescents use opioids during the immediate postoperative period, ranging from 8 to 16 tablets on average as demonstrated by our own preliminary investigations and published studies from other institutions.[27] Inclusion and exclusion criteria are presented in box 1. We will include English and Spanish-speaking participants. We will enroll participants from the outpatient surgery centres of two large academic paediatric medical centres on the West Coast of the United States.

Box 1 Eligibility criteria (children)

Inclusion criteria

⇒ 10–19 years old at the time of enrollment.

⇒ Scheduled for outpatient orthopaedic surgery of knee, shoulder or elbow.

Exclusion criteria

⇒ Serious comorbid mental health condition (eg, psychiatric admission in the past 30 days) impairing ability to participate in research.

⇒ Cognitive impairment (reported by clinician, parent or identified in medical charts) impairing ability to participate in research.

⇒ Serious comorbid physical impairment (reported by clinician, parent or identified in medical charts) impairing ability to participate in research.

⇒ Child or caregiver not proficient in English or Spanish.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Sample size

Power calculations and sample size estimations for this proposal are based on aim 1 and were estimated using preliminary data. Sample size estimation for aim 2 is difficult to compute because machine learning models are largely algorithmic based and not focused on frequentist statistical measures such as p values, nor do they focus on effect sizes. We estimated the sample size required to detect a change in the slope of the association between sleep deficiency parameters and the outcome of opioid use (SD=1.25) from our preliminary studies using a 5% type 1 error for a two-tailed test.[28 29] A sample size of 400 participants will allow us to detect a 25% increase in opioid use associated with severe sleep deficiency with 90% power. We will also detect a 25% increase in opioid use following surgery associated with a 2-point decrease in sleep quality and a 1-hour decrease in sleep duration.

Recruitment and enrollment

The research team will identify potentially eligible participants at the time that their surgery is scheduled using a custom-generated electronic medical record tool. Electronic medical records will be reviewed for eligibility. The study team, in collaboration with the clinical team, will

then approach eligible adolescents and their parents at least 10 days prior to surgery via an invitation letter to introduce the study. Study staff will contact interested participants to complete eligibility screening via phone. Study staff will obtain written consent (parents and youth ≥18 years) and assent (all youth) from interested families both verbally and online using forms in the Research Electronic Data Capture system (REDCap). The NIH, as funder of this research, issued a Certificate of Confidentiality protecting the privacy of research participants by prohibiting the disclosure of sensitive information.

Data collection methods

Schedule

The data collection schedule is presented in figure 1. Adolescents and parents will complete baseline surveys and adolescents will wear actigraphy devices for 7 days prior to surgery (T1). Immediately following surgery, starting on postoperative day 1, adolescents will complete four daily survey assessments and wear the actigraphy device for 14 days during the ecological momentary assessment phase of the study (T2). Opioid use will also be measured electronically for 14 days using eCap (T2). Adolescents and parents will complete follow-up surveys at 3 months (T3), 6 months (T4), 12 months (T5) and 24 months (T6) (figure 1.)

Actigraphy

Adolescents will complete actigraphy monitoring at T1 (7 days) and T2 (14 days) to assess sleep timing, continuity and patterns (ActLumus/ActTrust 2, Condor Instruments, São Paolo, Brazil). Actigraph devices are watch-like accelerometer devices worn on the wrist that collect sleep patterns over extended periods of time with minimal interference in participants' daily lives. Sleep and wake patterns are objectively captured based on activity detected by the accelerometer. Moreover, participants push an event marker on the device at bedtime and at wake time, and they also complete a corresponding sleep timing diary (via REDCap) each morning to report on the previous night's sleep timing (bedtime, time to fall asleep, number and duration of night awakenings, wake up time). To minimise scoring errors, we follow a standardised scoring protocol using actigraph activity and light data, along with event markers and sleep diary timing. Three actigraphy variables will be used in the primary analyses[30]: (1) total sleep time: this is the total duration in minutes classified as sleep from the onset to the offset of sleep. Sleep onset is defined as the first 10 min period with no more than one epoch of recorded activity, and sleep offset is defined as the last 10 min period with no more than one epoch of recorded activity. (2) Wake time after sleep onset: this refers to the number of minutes classified as wakefulness after the onset of night-time sleep. (3) Sleep efficiency: this is the ratio of total sleep time to the total time spent in bed at night, expressed as a percentage. Higher values indicate more efficient sleep, with values closer to 100% representing optimal sleep efficiency. Actigraphy monitoring has demonstrated feasibility and accuracy for assessing adolescent sleep patterns in the perioperative period based on studies performed in our lab.[31 32]

Ecological momentary assessment

Beginning on the first day following surgery, adolescents will complete electronic surveys during each of four predesignated time intervals (7:00–11:00, 11:00–15:00, 15–19:00 and 19:00–23:00) via REDCap for a 14-day period on their smartphones. EMA will include ratings of current pain intensity, mood and anxiety (11-point numeric rating scales (NRS, 0–10).[33–35] Participants who endorse opioid use will be asked to rate their subjective response following opioid use using the Opioid Drug Effects Questionnaire, including questions about opioid 'liking', 'disliking', feeling 'high' and whether they would like 'more' opioids. The United States Food and Drug Administration uses these scores as core outcomes in drug abuse liability research.[36] Sleep quality will be measured each morning using a REDCap sleep diary, with adolescents reporting global sleep quality experienced the prior night on an 11-point NRS (0–10).

Electronic monitoring of opioid use following surgery

Participants will be provided with an electronic medication bottle cap, eCap (Information Mediary Corporation), to monitor opioid use (both tablets and liquids) during the first 14 days following surgery. eCap, which appears like a standard medication bottle cap, fits on a standard medication vial and records the time and date when the vial is opened with a 99.6% event accuracy rate. Research staff will mail each participant an eCap-covered medication vial prior to surgery. Participants will be instructed to place their prescribed opioids in the vial following surgery. The research team will passively observe opioid use, meaning we will not provide any counselling regarding medication adherence to participants, nor will participants receive any advice regarding taking their opioid pain medications. Participants will be asked to remove opioids from the vial at the conclusion of 14 days of observations following surgery before mailing eCap back to the study team.

Survey measures

All survey assessments will be completed online through REDCap. Participants will receive email, text or phone reminders by research study staff to complete study measures if needed, ensuring all procedures are completed. Adolescent participants will be provided with a total of $180 (USD) in Amazon gift cards after completion of the study assessments: $40 is provided after T1, $60 after T2 and $20 for T3, T4, T5 and T6. Table 1 provides a summary of all survey measures.

Child self-report measures

Sleep quality: adolescent sleep quality will be measured using the PROMIS (Patient-Reported Outcomes

Table 1 Measures, domain and time points for data collection

Domain		Measure	Completed by	T1	T2	T3–T5	T6
Demographics	Biological sex, gender, race, ethnicity, family income, insurance status, parent education, housing, employment, income	Parent Background Questionnaire	Parent report	✔			
Medical history	Surgery type and anaesthesia technique	Child's electronic health record (EMR)	Data entered by the study team	✔			
Ecological momentary assessments	Pain intensity, anxiety, mood and subjective opioid effects	Numeric Rating Scale (NRS), 0–10	Daily diary: child		✔		
Child social factors	Tobacco, alcohol and drug use	Brief Screener for Tobacco, Alcohol and Drugs (BSTAD)	Child self-report	✔		✔	✔
	Family risk and protective factors	Family Risk and Protective Factors (FRPF)	Child self-report	✔		✔	✔
	Peer substance use	Peer Partner Substance use and Tolerance of Substance Use (PPSUTSU)	Child self-report	✔		✔	✔
	Alcohol and illegal drug availability	Perceived Availability of Illegal Drugs and Alcohol (PAIDA)	Child self-report	✔		✔	✔
	Perceived harm of substance use	Perceived Harm of Substance Use (PHSU)	Child self-report	✔		✔	✔
	Child experience of adverse childhood experiences (ACEs)	ACEs Questionnaire	Parent report	✔			
Child sleep	Sleep quality and patterns	Sleep diary	Daily diary: child	✔	✔		
	Sleep quality and patterns	Actigraphy	ActTrust II watch; Condor Instruments	✔	✔		
	Sleep quality and patterns	PROMIS: Sleep Disturbance Child (Short Form 8a)	Child self-report	✔		✔	✔
	Sleep deficiency	PROMIS: Pediatric Sleep Related Impairment (Short Form 8a)	Child self-report	✔		✔	✔
	Insomnia	Insomnia Severity Index Child	Child self-report	✔		✔	✔
	Circadian preference	Morning Eveningness Questionnaire Self-Assessment	Child self-report	✔		✔	✔
	Sleep-related disordered breathing	Pediatric Sleep Questionnaire: Sleep-Disordered Breathing Subscale	Parent self-report	✔		✔	
Child pain	Pain intensity	BPI: Brief Pain Inventory	Child self-report	✔		✔	✔
Child psychological factors	Symptoms of depression	Patient Health Questionnaire (PHQ-9)	Child self-report	✔		✔	✔

Continued

Table 1 Continued

Domain	Measure	Completed by	T1	T2	T3–T5	T6
	Symptoms of anxiety	PROMIS Pediatric Anxiety—Short Form 8a (V.2.0)	Child self-report	✓	✓	✓
Opioid use and misuse	Perioperative opioid use	Electronic pill cap	eCAP	✓		
	Opioid lifetime misuse	Opioids Lifetime Use	Child self-report	✓	✓	✓
	Prescription opioid misuse	YRBSS: Lifetime and Current Prescription Opioid Misuse	Child self-report	✓	✓	✓
	Prescription opioid use and availability at home	Parent Opioid Questionnaire	Parent self-report	✓		

Measurement Information System) Pediatric Sleep Disturbance (PSD) Short Form (V.1.0), which has demonstrated validity and reliability in samples of adolescents with and without sleep health issues in various clinical settings.[37 38] The 8-item self-report questionnaire asks participants to rate their perceptions of sleep quality, including difficulties falling and staying asleep, on a 5-point Likert scale from 1 (=never) to 5 (=always). Higher summed scores indicate worse perceptions of sleep quality. PROMIS scores are then converted to T-scores, using the appropriate scoring table provided by healthmeasure.net, which translates raw PROMIS score into a T-score with a mean of 50 and an SD of 10.

Sleep impairment: the PROMIS: Pediatric Sleep Related Impairment Short Form (V.1.0) is an 8-item self-report questionnaire that measures perceptions of daytime symptoms related to sleep deficiency. This measure has demonstrated validity and reliability in samples of adolescents with and without sleep health issues in various clinical settings.[37 38] Each item is rated by participants on a 5-point Likert scale from 0 (=never) to 5 (=always). A higher summed score indicates increased sleep deficiency. Similar to other PROMIS measures, these raw scores are then converted to T-scores using the healthmeasure.net website.

Insomnia: The Insomnia Severity Index (ISI) is a 7-item self-report questionnaire that measures insomnia severity and impact. The ISI has demonstrated good reliability and validity as a tool to screen for insomnia[39] and has been used in past research with adolescents.[40] Participants are asked to rate the severity of insomnia symptoms on a 5-point Likert scale from 0 (=none) to 4 (=very severe) as well as four additional items including sleep satisfaction, noticeability of insomnia to others, worry/distress over insomnia and insomnia interference with daily functioning. Higher summed scores indicate increased insomnia severity and impact.

Circadian preference: circadian preference will be evaluated with the Morningness-Eveningness Questionnaire for Children and Adolescents along with objective data on sleep using actigraphy.[41 42] Participants are asked to rate 19 items on various 4-point and 5-point Likert scales with the lowest values indicating evening types and the highest values indicating morning types. Summed scores indicate the following types: 16–30 (=definite evening), 31–41 (=moderate evening), 42–58 (=intermediate), 59–69 (=moderate morning) and 70–86 (=definite morning).

Pain questionnaire: The Pain Questionnaire is a 10-item self-report questionnaire that assesses the presence of pain and the body parts most affected. Youth are asked how long pain usually lasts (‘less than an hour’, ‘a few hours’, ‘half a day’ or ‘all day’) in addition to their usual pain intensity and their pain during rest and movement on an 11-point numeric rating scale (NRS, 0–10).[43] NRS for pain has been validated and is widely used to assess perioperative pain in adolescents.[33 34] Higher summed scores indicate higher pain intensity.

Youth report on the extent to which pain limited activities in the prior 7 days on a 0–100 visual analogue scale, with anchors 0='does not limit any activity' and 100='limits all activities'. Youth rate level of emotional upset due to pain during the preceding 7 days on a 5-point Likert scale with response options ranging from 'not at all' to 'very much', which are assigned values from 1 to 5.

Depressive mood symptoms: The Patient Health Questionnaire is a 9-item self-report questionnaire used to assess symptoms of depression.[44] Participants are asked to indicate how often each item applies to them during a 2-week period on a 4-point Likert scale from 0 (=not at all) to 3 (=nearly every day). Higher scores indicate higher severity of depressive symptoms.

Anxiety symptoms: The PROMIS Pediatric Anxiety-Short Form 8a (V.2.0) is an 8-item self-report questionnaire that evaluates anxious misery, fear and hyperarousal. Each item is rated by participants on a 6-point Likert scale from 0 (=never) to 5 (=almost always). A higher score indicates higher anxiety. This measure has demonstrated discriminant validity as well as reliability in adolescents.[45]

Adolescent substance use: The Brief Screener for Tobacco, Alcohol, and Drugs is used to identify adolescent exposure to and use of tobacco, alcohol and illicit drugs. This questionnaire is validated in adolescent clinical samples and demonstrates accuracy in identifying teens with and without substance use disorders.[46] Six yes/no items assess personal and friend substance use. For items answered 'yes' for personal use, participants selected which substances they used and the duration of use for each in the past year. Classifications of substance use include: no use, lower risk and higher risk.

Family risk and protective factors: The Family Risk and Protective Factors is a 38-item self-report questionnaire that was adapted from the Communities That Care Survey by the PhenX Substance use toolkit.[47] This measure assesses the level and prevalence of adolescents' exposure to substance use risk and protective factors in the family environment.[48 49] This measure can be used to identify the specific family-related elevated risk and depressed protective factors that can predict adolescent (and later life) substance use and abuse. Participants are asked to self-report the prevalence of their exposure to substance use risk and protective factors in the family environment on 4-point and 5-point Likert scales. Items are averaged for eight subscales that include categories such as 'Family Conflict', 'Attachment' and 'Parental Attitudes Favorable toward Drug Use'. Subscales are then further averaged to determine 'General Family Risk' and 'Family Drug Risk', with higher scores indicating higher risk.

Peer substance use: The Peer Partner Substance Use and Tolerance of Substance Use self-report questionnaire from the PhenX Substance Abuse and Addiction Collection[50 51] contains 22 items measuring the perception of friends' use of and attitudes towards substances. Participants are asked to identify the extent to which their friends use substances on a 5-point Likert scale from 1 (=none) to 5 (=all). Higher summed scores indicate higher substance use. Participants are also asked to identify how their friends would feel about the participant's own substance use on a 3-point Likert scale from 1 (=not disapprove) to 3 (=strongly disapprove). Higher summed scores indicate a lower tolerance of use.

Alcohol and illicit drug availability: The Perceived Availability of Illegal Drugs and Alcohol questionnaire from the PhenX Substance Abuse and Addiction Collection[50 51] is a 15-item self-report questionnaire that asks participants to assess the ease or difficulty of obtaining illegal substances from their community on a 5-point Likert scale from 1 (=probably impossible) to 5 (=very easy). Higher summed scores indicate higher availability.

Perceived harm of substance use (PHSU): The PHSU is a self-report questionnaire from the PhenX Substance Abuse and Addiction Collection.[50 51] Participants are asked to rate the perceived harms related to substance use through 11 items on a 4-point Likert scale from 1 (=no risk) to 4 (=great risk). Higher summed scores indicate higher perceived harm.

Parent measures

Child's experience of Adverse Childhood Experiences (ACEs): The ACEs Questionnaire is a 10-item parent-report questionnaire that assesses adverse childhood events, used by the National Survey of Children's Health. Five of the survey items, including: (1) divorce or separation of parent; (2) parent served time in jail; (3) child witnessed domestic violence; (4) lived with someone who was mentally ill or suicidal and (5) lived with someone with substance abuse problems, were adopted from the Behavioral Risk Factor Surveillance System ACE Module (Centers for Disease Control and Prevention). Additional survey items, including: (1) treated or judged unfairly due to race/ethnicity; (2) experienced death of parent; (3) child was a victim or witness of neighbourhood violence and (4) child suffered hardship due to low family income, were developed based on input from a technical expert panel involved with the National Survey of Children's Health to capture potentially stressful life-course events and experiences.[52] Some of the survey items used a Likert scale and responses categorised as 'somewhat often' or 'very often' were coded as a positive (yes) response and 'rarely' or 'never' as a negative (no) response. All ACEs will be categorised as binary (Y/N) and summed to calculate a composite score reflecting the number of ACEs each participant experienced.

Sleep-related breathing disorder (SRBD): parents or legal guardians will complete the Pediatric Sleep Questionnaire-SRBD Subscale, a 22-point parent-report questionnaire validated against polysomnography, multiple sleep latency test results (for the sleepiness subscale) and SRBD treatment (adenotonsillectomy) outcomes.[53] Parents or legal guardians are asked to rate their child's snoring, daytime sleepiness and hyperactivity and inattentiveness among other domains with ratings 'yes' (=1), 'no' (=0) and 'don't know' (=99). Higher

summed scores indicate a higher likelihood of the presence of sleep-disordered breathing.

Opioid use and availability at home: parents or legal guardians will complete the Parent Opioid Questionnaire to assess the availability of opioids in the home (yes/no), adolescent opioid prescription history (yes/no; once/more than once) and adolescent exposure to opioid or drug misuse through cohabitants (yes/no). Ratings of 'yes' are scored as 1 and 'no' as 0. A higher score indicates a higher exposure to opioids in the home.

Primary outcome measures

Opioid use following surgery

Our primary opioid use outcome is opioid use during the first 14 days following surgery, including number of doses (daily and total) and duration (time until opioid cessation) as measured using eCapTM. Persistent opioid use is defined ≥1 opioid prescription refill beyond 14 days after surgery. This time frame was conservatively chosen based on the expectation that standard management for the selected sports injury surgeries would not require opioid treatment for more than 14-day use.[54]

Opioid misuse

Prescription opioid misuse is defined as taking prescription or diverted prescription opioids (opioids not prescribed to the person using them) not in the way, for the reasons, in the amount, or during the time period prescribed. Adolescents will be surveyed about prescription opioid misuse before surgery and at each follow-up assessment using standardised questions directly obtained from the Youth Risk Behavior Survey[55] and NSDUH.[56] Adolescents will also be asked about their lifetime use, current use (past 30 days use), number of episodes, timing of last episode, sources of opioids for last misuse and motivations for misuse.

STATISTICAL METHODS

Our first aim is to test the direct and mediation pathways of sleep deficiency on opioid use following sports-injury surgery. We hypothesise that greater presurgery sleep deficiency, as measured by surveys and objectively monitored by actigraphy, will be associated with higher opioid use (daily doses and duration as continuous outcomes) over the first 14 days following surgery, and higher rates of persistent opioid use (binary outcome: yes/no) at 3 months. We will examine correlations between sleep variables and opioid use using univariate logistic regression for binary outcome or correlation analysis for continuous outcome. If univariate analyses identify significant associations between variables, we will apply multivariable regression analyses to further examine sleep deficiency as a predictor of opioid use, controlling for pain intensity and day fixed effects after surgery and clustering SEs for patient-level serial correlation in opioid use postsurgery to enable proper inferences.

We also hypothesise that during the first 14 days following surgery, greater sleep deficiency, as measured by the previous night's self-reported sleep quality and actigraphy monitoring, will be associated with higher opioid use (increased dose) during the following day. To assess time-varying associations between the prior night's sleep and the following day's opioid use in the 14 days following surgery, we will use lagged linear mixed effects regression. We will control for current day pain intensity, psychological factors and day fixed-effects after surgery and clustering SEs for patient-level serial correlation. Understanding associations between sleep, pain, psychological factors and opioid use are important components of the causal pathways between sleep and opioid use. To assess potential sensitivity to the misspecification of temporal lags, we will also use cross-lagged panel models with fixed effects to mitigate bias arising from reverse causality.[57 58]

Our third hypothesis related to aim 1 is that pain and psychological factors (mood, affect, subjective response to opioid use) will mediate the daily relationship between sleep deficiency and opioid use over the first 14 days following surgery. To test this hypothesis, our current plan is to examine direct associations and indirect associations using targeted maximum likelihood estimation (TMLE). However, the final and best estimation models will be determined once the data are analysed. Since this study uses an observational cohort design with no comparison group, these associations are not causal effects but will help inform what may happen if a clinician intervenes on sleep deficiency but does not directly intervene on pain intensity and psychological factors in future randomised trials. Our currently proposed approach requires no unmeasured confounding between the exposure and outcome, between mediators and the outcome, and between the exposure and mediators. In mediation analyses, TMLE estimation of direct and indirect associations has several key advantages, including requiring fewer assumptions, robustness to model misspecification and appropriate CI coverage even in finite samples.[59] Associations identified in our first aims will inform any alternative approaches that should be considered. This approach will be implemented using Stata and R statistical software and published TMLE code.[59]

Our second aim is to develop and validate a multivariable prediction model to identify adolescent patients at increased risk of prescription opioid misuse within 2 years following surgery. We hypothesise that greater sleep deficiency during the first 12 months following surgery, greater opioid use following surgery, a history of substance use, greater reported pain intensity and higher psychological distress following surgery will predict an increased risk for prescription opioid misuse at 24 months. To test this hypothesis, we will apply modern machine-learning algorithms. The primary outcome will be defined as any opioid misuse (yes/no) at 24 months following surgery. Many factors potentially predict opioid misuse and will be included in our models, including sociodemographic

variables, clinical factors, adverse childhood experiences, substance use history, psychological factors, sleep measures, pain measures and opioid use measures. Given the large number of potential predictors, we will apply modern machine learning algorithms to develop and validate the prediction model. Specifically, we will randomly split (eg, 75% vs 25%) the sample into training and validation samples. We will develop a prediction model based on the training sample, then assess the model performance on the validation sample. We plan to apply five popular machine learning algorithms, which include (1) penalised logistic regression, (2) gradient boosting machine learning, (3) artificial neural network with a single hidden layer, (4) linear support vector machine learning and (5) random forest.[60] Hyperparameters for each model will be optimised with three repeats of 10-fold cross-validation, then fit to the entire training sample. We will then assess each model by computing the area under the ROC curve on the validation sample. Predictive accuracy and misclassification rates will also be assessed. All analyses will be carried out using the R statistical software and related R packages. For model reporting, we will follow the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis reporting guideline.[61]

DISCUSSION

This study will provide novel information on how sleep deficiency prospectively impacts adolescent opioid use behaviours. This study will build on our prior research that demonstrated strong associations between sleep deficiency and opioid misuse behaviours in existing national samples of adolescents. Sleep deficiency is modifiable using existing behavioural interventions and therefore an appealing target for our future clinical trials to reduce adolescent opioid use and misuse following surgery.

Adolescence is a vulnerable period for initiating prescription opioid misuse due to the early maturation of reward-seeking brain centres relative to cognitive control.[62] Sleep and circadian rhythms also undergo significant changes during this time, with over 50% of adolescents reporting sleep deficiency.[63–65] Sleep deficiency enhances reward sensitivity and reduces cognitive control, increasing the risk of opioid misuse. Factors such as pain experience, depressive symptoms, anxiety, substance use and adverse childhood experiences, along with peer and family influences, further compound this risk.[8 66–69] While interventions to prevent opioid misuse have been designed for peer and family risk factors,[70] individual risk factors in the perioperative setting remain poorly described, limiting effective intervention development. Therefore, there is an urgent need to identify perioperative, modifiable risk factors so that adolescents at high risk for opioid misuse might be identified and offered preventive interventions.

Potential problems and mitigation strategies

Our observational cohort study involves enrolling and prospectively tracking adolescents over a 2-year period, which has several potential challenges. (1) Sample attrition is common to all longitudinal studies. However, this only becomes a problem if it is substantial and biases study findings. Our research team has significant experience with longitudinal studies and based on our prior studies, we expect to achieve 85% retention over 24 months. Strategies will include maintaining close contact with families via text and email, using remote data collection procedures, and providing adequate compensation. We have successfully used these strategies to achieve a >90% retention over the 12-month follow-up period in our preliminary study.[71] In addition, we will evaluate the potential threat to scientific validity by comparing outcomes among participants who drop out of the study to those who are retained. Any suspected biases will be considered when interpreting results. (2) Poor compliance is an acknowledged limitation of ecological momentary assessment protocols. To limit non-compliance, we have limited the frequency (4x per day) and time commitment (14 days) to within the limits suggested for adolescent EMA studies.[72] In addition, we encourage the use of the teen's own mobile device, have linked compliance to compensation and keep close contact with teens during the EMA study phase. Using these strategies, we have achieved 92.3% compliance with EMA procedures in our preliminary study, which is significantly higher than the 80% compliance rate recommended in the literature.[73] (3) Another potential challenge is the enrolment of surgical patients. We have accounted for this issue by estimating our recruitment rate based on our prior studies and by strongly collaborating with our surgical teams across two sites. Our timeline allows an extra 6 months for continued enrollment should we experience lower enrollment or higher attrition than expected. In addition, we will hold regular forums with the surgical teams to anticipate and address potential scheduling changes or recruitment challenges and discuss other issues.

Strengths

Our study has significant strengths and is an improvement in this area of research: (1) our prospective study design, in which parallel covariates are reliably and repeatedly measured over time, will allow us to look at changes over time in the same patient, defining the temporal sequence of changes and providing stronger evidence for causality than could be obtained from a cross-sectional design. (2) Our study employs electronic medication monitoring technology (eCap) to accurately measure opioid use after surgery. Unlike previous studies that used indirect methods like pill counts and self-reports, which aggregate data and introduce bias,[1 74 75] our approach directly records real-time medication use, minimising reporting bias. (3) We investigate how sleep deficiency prospectively predicts problematic opioid use and misuse in adolescents, postsurgery. Previous studies examining temporal

relationships between sleep and opioid use focused on adults in controlled laboratory environments,[76] which may not apply to adolescents or real-world clinical settings. Indeed, adolescence is the time period during life when sleep deficiency and problematic opioid use behaviours start. Our real-time assessments of sleep and opioid use in adolescents' natural environments provide novel insights into this high-risk group. (4) We use EMA methods to track sleep, pain, psychological factors and opioid use postsurgery. EMA allows for dynamic modelling of these relationships over time, overcoming biases inherent in cross-sectional studies. Additionally, EMA offers advantages over lab-based assessments, capturing the influence of environmental and internal factors on opioid use. Using actigraphy to measure sleep also provides a naturalistic assessment of sleep in the home environment.

Data management and analysis

Research data will be stored on secure servers that are compliant with the Health Insurance Portability and Accountability Act (HIPAA). These servers will be hosted, managed and monitored by Stanford University School of Medicine and Seattle Children's Research Institute. Data will be deidentified at the earliest possible opportunity. Participant contact information will be stored separately in secure, password-protected databases located on HIPAA-compliant servers at Stanford School of Medicine and Seattle Children's Research Institute. These databases will be linkable only by a unique study identifier.

Missing data and attrition

Missing data due to participant drop-out or non-compliance may have a significant effect on statistical power and on conclusions that can be drawn using statistical inference, particularly when data are systematically missing (ie, not random). We will first examine the amount and patterns of missingness. If missing at random is assumed and a substantial amount of missing data exists, we will conduct additional sensitivity analysis using multiple imputations with changed equations (MICE). Missing values are imputed based on the observed values for a given individual and the relations observed in the data for other participants, assuming the observed variables are included in the imputation model. The MICE approach is a flexible yet powerful technique to address missing data issues and has demonstrated excellent performance in practice. If missing not at random is suspected, the pattern mixture model will be used to estimate model parameters for different patterns of missing data and we will then combine the estimates over strata.[77]

Monitoring

This is a multisite observational study, with no interventions. There is no steering committee or data safety and monitoring board. The primary site is Stanford University School of Medicine, and the secondary site is Seattle Children's Hospital. The study team, including the principal investigator and clinical research coordinators from both sites, meets weekly to discuss study progress, maintenance of IRB approval and security of databases.

ETHICS AND DISSEMINATION

This study was approved by Advarra's Center for Institutional Review Board Intelligence (CIRBI). Stanford University relies on the Advarra IRB for all multisite NIH-funded clinical studies. Per NIH guidelines, all funded or supported studies conducting multisite or cooperative research need to have a single IRB. In this case, the single IRB service is provided by Advarra. Both the Stanford and Seattle sites rely on the Advarra IRB and have approved this protocol.

Study participants will be compensated for their time using Amazon gift cards. This is a minimal risk study. There are no hard copy records. All electronic data will be stored on institutional network drives with firewalls and security measures in place. Access to records and data will be limited to study personnel. Study data will be deidentified and a master linking log with identifiers will be kept and stored separately from the data. Findings will be communicated via publication in peer-reviewed journals and presentations at professional society meetings.

Study status

Recruitment started in March 2024. The current approved protocol is V.1.02 (Initial submission approval date: July 2023; approved version at final journal submission: 1 August 2024). While this study does not include an intervention, we followed study protocol reporting guidance as provided by the Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines (see online supplemental file 1). Recruitment is estimated to be complete by March 2028. Any protocol modifications will be approved by Advarra's IRB and updated on the participants' consent form.

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