Behavioral Treatment of Narcolepsy-Related Nightmares

NCT05709873

Study Protocol and Data Analysis Plan

October 29, 2024

METHODS

The trial was conducted using a multiple baseline single-case experimental design (SCED). For early phase behavioural treatment research, this methodology is preferred to small pilot studies because the latter are typically underpowered to detect a treatment effect and do not produce reliable effect sizes to power future larger trials (Czajkowski & Hunter, 2021; Epstein et al., 2021; National Center for Complementary and Integrative Health, 2020). Furthermore, in SCEDs the baseline period serves as the control, providing strong internal validity and allowing for a determination that the intervention resulted in the observed changes (Epstein et al., 2021). Replication of effects across patients provides preliminary external validity.

Study assessments were completed using REDCap electronic data capture tools hosted at Northwestern University (Harris et al., 2009; Harris et al., 2019). Participants were randomised to a baseline period of 2 or 4 weeks. Since symptoms were assessed via daily diaries, there were 14 or 28 data points during the baseline period. Varying the length of the baseline facilitates an assessment as to whether changes in symptoms occur when, and only when, treatment is introduced. After the baseline period, all participants received treatment followed by a 2 week posttreatment period. Treatment was assigned based on the location of the participant, since CBT-N sessions were conducted via telehealth, but targeted lucidity reactivation (TLR) required an in-person visit (those outside of the Chicago area received CBT-N, those in the Chicago area received CBT-N + TLR).

Eligibility, recruitment, and screening

Individuals were eligible to participate if they met the following criteria: (a) diagnosis of narcolepsy (confirmed via clinical documentation provided by participant), (b) age 18 or older, (c) living in the United States, (d) receiving standard care for narcolepsy, (e) sleep and psychiatric medications stable for at least 3 months and willing to keep medications stable throughout the study (so that changes in symptoms could be attributed to the study intervention rather than changes in medications), (f) nightmare frequency of ≥3 times per week, and (g) Disturbing Dream and Nightmare Severity Index indicating probable nightmare disorder (score > 10). Individuals were excluded for the following: (a) currently engaged in sleep- or trauma-focused psychotherapy; (b) previous behavioural treatment for nightmares; (c) medical, psychiatric, or cognitive condition which would interfere with the ability to engage in the treatment; and (d) untreated sleep apnea, given evidence that this can cause or exacerbate nightmares (BaHammam & Almeneessier, 2019; McCall & Watson, 2022). For participants residing in the Chicago area who would be assigned to the CBT-N + TLR condition, the following additional criteria were applied: (a) able to attend an in-person study appointment; (b) able and willing to not take any stimulants or wake-promoting medications prior to arrival on day of laboratory visit, and (c) no history of epilepsy.

Participants were recruited through hypersomnia advocacy organisations, social media, and local sleep clinics. Potential participants completed a screening survey to determine preliminary eligibility and then completed an interview to collect additional information on medical and psychiatric history, including the Quick Structured Clinical Interview for DSM-5 Disorders (QuickSCID-5) (First & Williams, 2021). The posttraumatic stress disorder (PTSD) module was administered in order to characterise the presence of PTSD in the sample, and the following additional QuicSCID-5 modules were administered to screen for comorbidities that might affect

nightmares or interfere with the ability to engage in the study: bipolar disorder, psychotic symptoms, alcohol use disorder, nonalcohol substance use, and obsessive-compulsive disorder.

Treatment

Cognitive behavioural therapy for nightmares (CBT-N)

All participants received CBT-N (Pruiksma et al., 2023) which was modified for narcolepsy and delivered by a board-certified sleep psychologist (JMM) via videoconference during weekly 1 h sessions. Participants in the CBT-N group completed seven therapy sessions, while those in the CBT-N + TLR group completed six therapy sessions and one session of TLR. In addition to the core techniques of nightmare rescripting and imagery rehearsal which are included in various iterations of IRT, CBT-N includes other cognitive and behavioural components to address factors that perpetuate nightmares. Modifications for narcolepsy were created in consultation with a narcolepsy patient advocate who is a licensed therapist with experience treating nightmares.

Targeted lucidity reactivation (TLR)

For session six of the treatment, participants who received TLR completed a 4 h daytime session at the research laboratory. Procedures were based on prior studies (Carr et al., 2020; Konkoly et al., 2021) and involved a training period prior to sleeping while being monitored via polysomnography (electroencephalography, electrooculography, chin electromyography, nasal cannula). This procedure took place during a daytime nap given that participants with narcolepsy were expected to be able to nap easily. They were instructed not to take any stimulants or wake promoting medications on the day of the visit.

The week prior – during the fifth treatment session – the procedures and purpose of TLR were explained to participants and several aspects of the procedures were practised, including the lucidity training procedure in which participants were taught to associate a sound (the TLR cue; three pure-tone beeps increasing in pitch [400, 600, and 800 Hz] lasting approximately 650 ms) with a lucid state of mind. Participants also practised performing signals to indicate if they were lucid (moving eyes left–right–left–right) or rescripting a dream (sniffing in-out-in-out). Because of the therapeutic aim of this study, participants were also trained to associate an additional sound cue with their rescripted dream, thus for the week prior to TLR they were instructed to listen to a sound recording (1 s C69 piano chord repeating every 10 s) while practising imagery rehearsal (Schwartz et al., 2022). Finally, another sound cue associated with the rescripted dream was recorded by the therapist, and this consisted of 2–3 words chosen by the participant which represented the positive themes of their rescripted dream.

Upon arrival at the laboratory for the TLR session, participants were prepared for polysomnography and then underwent a pre-nap training period in which they were trained to associate the TLR cue with a lucid state. To prevent the participant from falling asleep prematurely, they initially practised while sitting up with the lights on and the instructions were given while maintaining eye contact. Then, while lying down and with lights off, the lucidity sound cue was repeated at increasing intervals as the participant fell asleep and played again when the participant entered REM sleep. Once in REM sleep, C69 and verbal cues associated with dream rescripting were also played. When participants woke during the nap, a verbal dream report was collected and

then they were allowed to resume sleeping if there was still time remaining in the session. One week following the laboratory visit, participants completed the final treatment session with the study therapist. In addition to covering standard content for the final session of CBT-N, this session included discussion of the participant's experience with TLR and how they could apply it to future nightmares.

Measures

Sleep diary

Participants completed a daily sleep diary (see Appendix A) at baseline, during treatment, and at posttreatment. The sleep diary captured the frequency and severity of nightmares as well as the frequency of other REM-related disturbances often seen in narcolepsy: sleep paralysis, sleep-related hallucinations, dream enactment, sleep talking, lucid dreams without control, and lucid dreams with control. Participants also estimated the duration of awakenings (wake time after sleep onset; WASO) that were caused by nightmares. For nightmare severity, participants were asked to indicate how severe their nightmares were overall each day (1 = not at all, 2 = slightly, 3 = moderately, 4 = very much, 5 = extremely). For nightmare frequency, participants were asked to note the number they had which did and did not wake them, and both were counted toward the frequency of nightmares used in analyses. By definition nightmares often (but not always) cause an awakening (Garriques et al., 2024), and we deemed it important to include both in the context of narcolepsy because features of narcolepsy make it less likely that awakenings will always be clearly discernable and recollected. Namely, (a) the boundaries of sleep/wake states are more permeable in narcolepsy and (b) brief awakenings are less likely to be recalled, and narcolepsy may make resuming sleep quickly after a nightmare easy (or unavoidable) despite emotional distress.

Questionnaires

During the baseline and posttreatment periods, participants completed an assessment which included the following measures: Disturbing Dream and Nightmare Severity Index (DDNSI) (Krakow, 2006), Nightmare Disorder Index (NDI) (Dietch et al., 2021), Epworth Sleepiness Scale (ESS) (Johns, 1991), Hypersomnia Severity Index (HSI) (Kaplan et al., 2019), Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10) (Chasens et al., 2009), Paris Arousal Disorders Severity Scale (1-month version; PADSS) (Arnulf et al., 2014; van Mierlo et al., 2022), Lucid Dreaming Skills Questionnaire (LUSK; modified to reflect a 1 month time period) (Schredl et al., 2018), Patient-Reported Outcomes Measurement Information System (PROMIS) Depression (Pilkonis et al., 2011), PROMIS Anxiety (Pilkonis et al., 2011), PROMIS General Self-Efficacy (Salsman et al., 2019), and PROMIS Self-Efficacy for Managing Symptoms (Gruber-Baldini et al., 2017). A new scale was created for this study (with input from two individuals with narcolepsy) to assess the frequency of dream delusions and resulting distress (see Appendix B –Dream Delusions Scale). In order to gauge whether the length of the assessments was acceptable or burdensome to participants with narcolepsy (to inform future trials), we asked a single item at each assessment regarding its length (see Appendix C). At posttreatment, participants also completed the Client Satisfaction Questionnaire (CSQ) (Larsen et al., 1979) and an exit interview with a study coordinator to obtain feedback on the treatment.

DATA ANALYSIS PLAN

The six participants who completed the study were included in data analyses. Nightmare frequency and severity (from sleep diaries and the DDNSI) were the primary outcomes. Examination of nightmare frequency and three narcolepsy-related symptoms from sleep diaries (sleep paralysis, sleep-related hallucinations, and dream enactment) was conducted in accordance with established guidelines for analysing SCED data using both visual inspection and statistical methods (Barlow et al., 2009). Visual inspection is considered a conservative approach to data analysis in SCED. To conduct between- and within- subject visual inspection analyses data were plotted graphically and visually assessed for changes across study phases. Changes in level (i.e., mean of outcomes measures) across phases indicate the magnitude of treatment effects. Changes in slope indicate the rate of change. For ease of viewing, the data points in figures for visual inspection represent weekly means for the daily sleep diary data. In addition to visual inspection, effect sizes were calculated to estimate the magnitude of change using the between-case standardised mean difference (BC-SMD), which accounts for small sample sizes and is interpreted in the same manner as Cohen's *d* (0.2 = small, 0.5 = medium, 0.8 = large) (Cohen, 1988; Valentine et al., 2016). Using the web-based program scdhlm (Pustejovsky et al., 2023; Valentine et al., 2016), effect sizes were calculated for all sleep diary outcomes from baseline to treatment and from baseline to posttreatment. Given the small sample size, effect sizes were calculated for the total sample rather than each treatment group separately. An effect size was considered statistically significant at $p < 0.05$ if the 95% confidence interval (CI) did not include zero. Changes from baseline to posttreatment on the DDNSI and other questionnaires were examined using the Wilcoxon signed-rank test. For this test, an effect size *r* of 0.1 is considered a small effect, 0.3 is medium, and 0.5 is large (Cohen, 1988).