Empower Opioid Misuse & Chronic Pain (RAP_EOM)
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Study Protocol

This pilot study aims to examine the feasibility, acceptability, and preliminarily examine efficacy of transcutaneous electrical nerve stimulation (TENS) at the ulnar nerve, in reducing opioid craving and use and decreasing pain. Opioid prescribing for chronic pain has increased dramatically over the past several decades, with devastating public health consequences, including high rates of opioid misuse and overdose deaths. Safe nonpharmacological treatments are urgently needed. Preclinical studies have shown that peripheral nerve stimulation at the ulnar nerve (ulnar aspect of the palm) through acupuncture or electrical stimulation directly regulates the mesolimbic dopaminergic pathway and reduces addictive behaviors. In addition, neurostimulation at acupressure points may reduce some types of chronic pain. Empower (TheraNova, LLC) is a non-invasive, portable TENS device that provides electrical stimulation at the ulnar nerve, which may reduce cravings and improve pain. We propose a single-blind, randomized controlled trial to examine the feasibility and to preliminarily examine efficacy of Empower in reducing opioid craving and opioid use in Veterans with chronic non-cancer pain (NCP). Aims are to examine the feasibility and acceptability of Empower and preliminarily examine its efficacy in reducing cravings, decreasing opioid use, and reducing pain when used at the ulnar nerve. Up to thirty veterans with chronic NCP and opioid misuse will be recruited. On Days 1- 7, participants will undergo baseline monitoring, and on Days 8-21, participants will undergo daily neurostimulation at ulnar nerve (n=15) or a control acupoint on the dorsal bicep (n=15). Study procedures will occur at home over 3 weeks, through secure two-way video or phone conference, with outcome assessments occurring at Days 0, 7, and 21. Pain scores, craving, and opioid use will be measured daily Days 0-21. Our goal is to provide an intervention that, alone or in conjunction with current treatments, reduces craving and reduces reliance on opioids in high-risk chronic pain patients.

PROCEDURE

In this proof-of-concept study, we will use a single-blind, randomized controlled design to assess feasibility, acceptability, and preliminarily examine efficacy of Empower in reducing opioid craving, opioid use, and pain levels in 30 Veterans with chronic NCP and opioid misuse. After screening, participants will undergo a 7-day no-treatment Baseline Monitoring Period, during which they will complete daily self-report measures of craving and pain. Participants will then take home the Empower device over a 14-day intervention period, during which they will receive neurostimulation at the ulnar nerve (n=15) or neurostimulation at a different anatomical location (Dorsal bicep) (n=15), twice daily, for 15 min on each side of the body (30 min per treatment; 60 min total per day). Study procedures will occur over 3 weeks, with in-clinic assessments occurring at or around Days 0, 7, 14, and 21. Primary outcomes include: opioid craving, prescribed and nonprescribed opioid use, and pain scores; and qualitative and quantitative measures of usability and acceptability at treatment end. Exploratory outcomes include self-reported depression levels, activity scores, and health-related quality of life, and the association between pain scores and craving levels over time.

The total duration of participant participation will be three weeks. At screening, self-report and interviewer data will be reviewed to determine participant eligibility. Medical conditions, psychiatric history, and medication list will be collected through review of participants' VA medical records. Participants will complete the MINI Neuropsychiatric Inventory. Urine toxicology panels may be completed through either VA lab urine drug screen or urine drug screen home test kits for participants at Days 0, 7, and 21. During pandemic times, if a participant is already scheduled for an essential visit to the hospital and lab, then they may optionally take the test at the lab. However, due to pandemic restrictions, we will also offer at home test kits for participants who will not be attending the VA site for an essential

visit. To encourage self-monitoring during treatment sessions, participants may optionally self-monitor heart rate variability, through their own at-home heart rate monitors or through provision of commercialized heart rate monitoring apps. Interested participants will be informed that they may optionally monitor heart rate before, during, or after treatment sessions at Days 0, 7, 14, and 21, from home. Readings will be collected via encrypted message, de-identified and stored in the password protected database.

A urine pregnancy test in women ages 18-50 who do not confirm a reliable method of birth control at screening will also be completed at screening (Day 0), either in the VA lab or at home. The results of at home urine pregnancy test can be shared securely via encrypted email through a photo image of the home test. We will obtain informed verbal consent to communicate with each participant's medical provider to confirm eligibility after verbal consent. Participants who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study.

The first week (Days 0-7) will be the Baseline Monitoring Phase, in which baseline measures of craving, and pain are completed daily (see below). On Day 7, participants will be randomized to use the Empower device at the ulnar nerve (Treatment Group, n=15) or at the bicep (Sham Group, n=15). The subsequent two weeks will be the Treatment Phase, followed by the Post-Treatment Completion visit at the end of the two- week Treatment Phase. Throughout the study, the participant will complete daily surveys on the Empower app on the provided smartphone and weekly Qualtrics-based questionnaires. The participant will be asked to complete surveys as close as possible to awakening. During the Treatment Phase only, the participant will self-administer a 30-minute treatment two times daily. The participant will be asked to administer treatments approximately 12 hours apart, if possible. The smartphone will have daily notifications to remind the participant to complete surveys and treatments.

The study will include three clinic visits:
1) Enrollment and start of Baseline Phase (Day 0),
2) Completion of the Baseline Phase and start of the Treatment Phase (Day 7, ± 5 days to account for scheduling/ weekends), and
3) Study Completion (14 ± 5 days after Visit 2).

At Baseline (Day 0), the participant will be given the smartphone with Empower app and trained on smartphone and app use. The participant will then be sent home with the smartphone and instructions for use. They will record craving levels and pain levels daily on the Empower app. On Day 7, the study team will use a secure two-way video or telephone conference app to randomize participants into one of two groups (treatment condition (palm) or control condition (dorsal bicep) in a 1:1 ratio according to a computer-generated code provided by the study biostatistician using randomization software. Participants will be randomized in blocks of random size ranging between 4 and 6 to ensure equal numbers in each group and to maintain relative balance between groups as the study progresses. After enrolling a participant into the study, all study materials and devices will be securely delivered to the participant. When the receipt of the materials is confirmed with the participant, study staff will coordinate a tutorial on how to use the device using secure two-way video or telephone conferencing. Once participants demonstrate an understanding for how to use the Empower Neuromodulation System at their designated site, they will then undergo their first self-administered electrostimulation session under study staff supervision.

Starting on Day 8, all participants will self-administer neurostimulation via Empower upon awakening (immediately following completion of the Empower App self-reports) and again approximately 12 hours later. Treatment Condition: Participants will complete a 15-min electrical stimulation application via

Empower on one palm (ulnar nerve acupoint) followed by an additional 15-min stimulation on the opposite palm (30 min per session, 60 min per day). Control Condition: Empower will deliver equal electrical current to the dorsal aspect of the bicep for equal time duration as the Treatment condition.

Surveys administered through Qualtrics will be conducted through secure two-way conferencing or encrypted e-mailed to participants through Qualtrics. The e-mails will contain no health information and will only contain the link to the survey in which a participant will submit their responses, and what week of the study they are in. The survey links will be anonymized as to not retrieve any IP address information from participants and will also be de-identified and participants will be entering their subject ID numbers rather than any identifiable information. The e-mail will be sent from a no-reply Qualtrics server. At the final assessment day, after the participant has completed their last self-administered treatment session, the clinical research staff will determine if any adverse effects (AEs), serious adverse effects, SAEs, or UADEs or other side effects have occurred during the study. The participant will also complete the weekly measures along with the usability survey on Qualtrics.

Statistical Analysis Plan

Prior to analysis, all data will be examined for anomalous and missing values and described in detail. To address missing data, we will perform a sensitivity analysis using a "copy reference" approach, under which missing-at-random data in either condition is imputed. The description of the data is a key aspect of this work as it informs future studies. Aim 1: Measures of feasibility, including proportion of those eligible among those screened, proportion enrolled among those eligible, enrollment rate, study retention, adherence to the baseline monitoring period, adherence to the treatment and control conditions, study completion rate, and potential adverse effects will be calculated. We will also passively collect data about participant usage patterns (compliance and electrical current). Qualitative data examining acceptability will be analyzed using an iterative, inductive process. We will meet approximately biweekly to conduct multiple reviews to identify prominent themes and develop coding templates based on new data emerging from interviews and using grounded theory methodologies. Mean quantitative acceptability data will be calculated, with a target of SUS $\geq$ 70 and CSQ $\geq$ 24. Lower scores would lead to revision of product design or other features to improve acceptability.

Aims 2-3 and Exploratory Aims: Outcome measures will be examined with a series of parallel statistical models, estimated via maximum likelihood, using planned contrasts between the Empower active ulnar nerve treatment condition, the control condition, and the baseline monitoring period. Analyses of in-clinic assessments will compare outcome measures at Days 0, 7, 14, and 21. Given the limited number of assessment points, the most parsimonious model will be a general linear model for each outcome measure. For the daily measures, we will use multilevel modeling to compare changes in variables over days between the treatment and control condition/baseline monitoring period. Analyses will be performed with SPSS.