Title: Extended Home-use Trial of a Novel Device to Reduce Chronic Neuropathic Pain
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Extended home-use trial of a novel device to reduce chronic pain

1. BACKGROUND

Device Description and Mechanism of Action:

The Sana Pain Reliever (Sana PR) by Sana Health Inc is a device comprised of one (1) main component (Mask with Earbuds) and two (2) ancillary components (Charger and Headband). The device is worn over the eyes (with earbuds in ears). The device pulses light at a single wavelength but various frequencies throughout a specific firmware algorithm. Through the earbuds, the device also plays different tones in conjunction with the pulses. The device has a skin contacting Heart Rate Variability (HRV) sensor built into the forehead area that measures HRV throughout use.

The underlying mechanism of action for the Sana PR is Audio Visual Stimulation (AVS), a form of neurofeedback and a non-pharmacological intervention that has been used for both performance enhancement and symptom management. Light and Sound stimulation has been used for over 100 years. In the early 1930s, it was reported that light and sounds stimulation could change the rhythm of brain activity, termed "entrainment". As progress was made in this field, several clinical applications of the photic and sound stimulation were studied, including; attention deficit and hyperactivity disorder, cognitive enhancement, migraine headaches, stress, and pain management. Brain activity can be tracked through brainwaves, which represent the electrical firing of the neurons of the central nervous system and can be measured by electroencephalogram (EEG). It is through these electrical signals that the brain communicates within itself and with other organ systems. Five common brainwave bandwidths (delta, theta, alpha, beta and gamma) and the related mental activities have been well described. Within the five common brainwave bandwidths, sub categories (high, low alpha and beta, and sensorimotor rhythm) have been identified for different mental activities. Specifically, delta activity (0.5–3Hz) is dominant primarily during deep sleep. Theta activity (4 – 7Hz) is typically seen in drowsy and relaxed states. Low alpha (8–10Hz) is the dominant brainwave bandwidth observed during meditation and the state of turning inward (daydreams, dissociation from external stimulation).

When the brain is given a stimulus, through the eyes or ears, it emits a responsive electrical charge, called a Cortical Evoked Response. These electrical responses, measured via electrodes, travel throughout the brain and is ultimately perceived as vision and audible sound. When the input stimulus resembles a pattern the brain itself uses, the brain responds by synchronizing to it, a process called Frequency Following Response (FFR). The Sana Mask utilizes this above described AVS mechanism to induce FFR. The firmware consists of periods of light/sound pulsing at three distinct pulse frequencies; ~8Hz, 3Hz, and 1Hz. For each frequency, there are distinct sections where the audio and visual pulses vary from eye to eye, and ear to ear.

The website for the device can be found here: https://www.sana.io/

Previous Trials Using the Sana PR:

The Sana Pain Reliever device has been in a previous study entitled "Photic Sleep Enhancement During a Mars Analog Exploratory Mission Simulation" that received a Western Institutional Review Board Certificate of Approval (attached). Two abstracts from studies involving the device are also attached.

2. Objectives

Primary: Determine the effectiveness of the Sana PR at reducing chronic pain over an 8-week intervention period and the long-lasting effect of pain relief at a 4-week follow-up using the following outcome measures:

Secondary Objectives:

1) Determine the impact using the device for an 8-week intervention has on Quality of Life and Sleep

2) At both baseline visits and both follow-up visits participants will complete a body chart on pen and paper to draw out where they feel their pain. Changes to the location of their pain will be measured.

3) Determine the tolerability and user acceptability of the devices

3. Device

The Sana Pain Reliever (Sana PR) by Sana Health Inc is a device comprised of one (1) main component (Mask with Earbuds) and two (2) ancillary components (Charger and Headband). The device is worn over the eyes (with earbuds in ears). The device pulses light at a single wavelength but various frequencies throughout a specific firmware algorithm. Through the earbuds, the device also plays different tones in conjunction with the pulses. The device has a skin contacting Heart Rate Variability (HRV) sensor built into the forehead area that measures HRV throughout use.

Figure 1: the Sana mask

4. Study Procedures

Description of the Study Design

Design:

Double blind, randomized, sham-controlled trial parallel arm study that will assess the effectiveness and patient perception of the benefit of the Sana Pain Reliever in individuals with chronic pain.

Device:
The Sana Pain Reliever (Sana PR) by Sana Health Inc is a device comprised of one (1) main component (Mask with Earbuds) and two (2) ancillary components (Charger and Headband). The device is worn over the eyes (with earbuds in ears). The device pulses light at a single wavelength but various frequencies throughout a specific firmware algorithm. Through the earbuds, the device also plays different tones in conjunction with the pulses. The device has a skin contacting Heart Rate Variability (HRV) sensor built into the forehead area that measures HRV throughout use.
- Real Arm
Each session with the device will last 15 min and run under the device's normal settings. The session consists of periods of light/sound pulsing at three distinct pulse frequencies; ~8Hz, 3Hz, and 1Hz. For each frequency, there are distinct sections where the audio and visual pulses vary from eye to eye, and ear to ear.
- Sham Arm
Each session with the device will last 15 min and run under the device's sham setting. For the Sham arm, the device will have the light on for 5 min, off for 5 min and then on again for 5 min. Ear plugs will be used in place of headphones. There will be no sound from the device in the sham group.

Application:
The application being used in this study was designed by Sana health specifically for this study. The application controls the Sana Pain Reliever device and allows users to use the device. Users must use the application to start each session with the device, but the device permits multiple, sequential uses of the device without requiring an interaction with the application. The application will be given to participants of this study on a tablet device. Participants will also be given the charging equipment for the device. The application is HIPAA compliant and will undergo InfoSec review at Mount Sinai. Participants will use the application on a tablet device that will be loaned to them for the duration of the study. The application will track data for this study during the at-home portions of the study between the two baseline visits, over the course of the intervention and between the follow-up visits.

- At-home intervention period (week 2 - 10) - tablet and Sana device:
The application tracks the number of times the device is used in a day and time stamps those sessions. For each session, the application records the HRV data from the forehead sensor of the device and what frequency the auditory and visual stimuli the device emitted during the 15 minutes. Prior to and immediately after each session the application will ask users to rate the amount of pain they are feeling in the moment on a Visual Analog Scale (VAS) along a number line from "no pain" to "worst imaginable pain". The first time the device is used each day, participants will be asked to complete a VAS for how they slept from the night prior. For the last use of the device prior to going to sleep for the day, participants will only be asked to complete the VAS prior to using the device to not disrupt sleep patterns. Additionally, at the last use before sleep participants will be asked to select which of their medication for pain management they took that day. The medications will appear in a drop-down menu on the application. Medications will be reported by each individual to the research team at the first baseline visit week 0 and will be inputted by the research team into each participant's application. Every two weeks during the 8-week intervention period the application will also prompt users to complete the following additional questionnaires: the Neuropathic Pain Symptom Inventory, the Pittsburgh Sleep Quality Index and Patient Health Questionnaire Type 9 for Depression (PHQ-9) and the General Anxiety Disorder 7-item questionnaire (GAD-7). A reminder to complete these biweekly questionnaires will be sent to participant's cell phones via text message and on the tablets themselves. Additionally the application will send compliance messages to participants if participants do not fill out the fortnightly questionnaires.

- Between baseline visits (week 0 – 2) and between follow-up visits (week 10 -14) monitoring of pain at home – tablet only .

During these time periods participants will be asked to use the tablet with the application daily at night prior to sleep. Participants will be asked to complete a VAS of how they slept the night prior, a VAS of pain and asked to report the medications they used that day for pain management.

Description of Procedures Being Performed

Informed Consent: Participants who fulfill the inclusion/exclusion criteria will be consented to the study at the Abilities Research Center at the start of their first in-person study visit or remotely via a telephone call to talk through the consent form followed by completion of the E-Consent process ahead of their first teleconferenced study visit.

Study devices (mask and tablet) will be shipped together ahead of the first visit for those not completing in-person visits. They will be activated and deactivated remotely at the appropriate times. Those completing study visits in person will receive and return their devices at different stages of the trial (described below).

INITIAL BASELINE CLINICAL ASSESSMENT (Week 0) - AT THE ARC OR VIA VIDEO CALL
Screening: After consent has been obtained participants will complete the Beck Depression Inventory (BDI) at the initial baseline visit. Individuals who score greater than 30 pts on the scale (Severe or Extreme Depression) will be withdrawn from the study.

Participant Information will be collected including:
- Age, gender, name and contact information (phone number(s) and email address).
- Current medications: the list of medications will be collected to add to each participant's Sana Health application. - A self-reported medical history
- Documentation of the location of their pain on a body chart
- Documentation of what pain management techniques participants typically use
Participants will then complete the following questionnaires: - Neuropathic Pain Symptom Inventory (NPSI)
- Pittsburgh Sleep Quality Index (PSQI)
- Beck Depression Inventory (BDI)
- Patient health Questionnaire Type 9 for Depression (PHQ-9)
- General Anxiety Disorder 7-item questionnaire (GAD-7)
- World Health Organization Quality of Life BREF (WHOQOL-BREF) & World Health Organization Quality of Life Pain (WHOQOL-pain)

Study Devices: Participants will be loaned a tablet device with the Sana application installed. Participants will be instructed on how to use the device and application.

BASELINE PAIN MONITORING (Week 0 - 2) - AT THE HOMES OF THE PARTICIPANTS
Participants will be asked to use the study tablet with the Sana application daily, at night prior to going to sleep. Participants will be asked to complete a Visual Analog Scale (VAS) of how they slept the night prior, a VAS of their amount of pain and asked to report the medications and strategies they used that day for pain management.

SECOND BASELINE CLINICAL ASSESSMENT (Week 2) - AT THE ARC OR VIA VIDEO CALL
Participant Information will be collected including:
- Record of changes in medications
- Record of changes in pain management techniques participants typically used - Documentation of the location of their pain on a body chart
Participants will then complete the following questionnaires: - Neuropathic Pain Symptom Inventory (NPSI)
- Pittsburgh Sleep Quality Index (PSQI)
- Beck Depression Inventory (BDI)

- Patient health Questionnaire Type 9 for Depression (PHQ-9)
- General Anxiety Disorder 7-item questionnaire (GAD-7)
- World Health Organization Quality of Life BREF (WHOQOL-BREF) & World Health Organization Quality of Life Pain
(WHOQOL-pain)

Study Devices: Participants will be randomized into the Sham or Real study group arm and will undergo a Sana PR familiarization session:

ARM 1: Real

- Participants will be loaned a Sana PR device, headphones, charging cables and a strap to secure the device on
their head
- The research team will download the Sana Health application on a tablet device compatible with the application that
will be loaned to participants (this device will be a tablet that has all functions not necessary to the functionality of the
Sana application disabled). The device will be loaned to participants for the duration of the 8-week intervention. - The research team will teach the participant how to use the Sana PR device and the Sana Health application.
Participants will be given an instruction manual for the device and mobile application. Participants will be instructed to call the lab's direct phone-line (212) 824-8369 if they have any additional questions when using the device at home.
- Participants will then complete their first 15 min session with the device in its normal settings under the supervision of the research team. For the Real arm, the session with the devices consists of periods of light/sound pulsing
at three distinct pulse frequencies; ~8Hz, 3Hz, and 1Hz. For each frequency, there are distinct sections where
the audio and visual pulses vary from eye to eye, and ear to ear. This first session will ensure the subjects know how to properly use the devices and that there are not any adverse events (AEs) from the first use of the device. Participants will be instructed to call the lab's direct phone-line (212) 824-8369 if they experience an AE when using the device at home.

ARM 2: Sham

- Participants will be loaned a Sana PR device, earplugs, a charging cable and a strap to secure the device on their
head
- The research team will download the Sana Health The research team will download the Sana Health application
on a tablet device compatible with the application that will be loaned to participants (this device will be a tablet that has all functions not necessary to the functionality of the Sana application disabled). The device will be loaned to participants for the duration of the 8-week intervention.
- The research team will teach the participant how to use the Sana PR device and the Sana Health application. Participants will be given an instruction manual for the device and mobile application. Participants will be instructed to call the lab's direct phone-line (212) 824-8369 if they have any additional questions when using the device at home.
- Participants will then complete their first 15 min session under the supervision of the research team. For the Sham arm, the device will have the light on for 5 min, off for 5 min and then on again for 5 min. Ear plugs will be used in place of headphones. There will be no sound from the device in the sham group. This familiarity session will ensure the subjects know how to properly use the devices and that there are not

any adverse events (AEs) from the first use of the device. Participants will be instructed to call the lab's direct phone-line (212) 824-8369 if they experience an AE when using the device at home.
Safety monitoring: A member of the research team will call the participant 48 hours after the first session with device to check for AEs, difficulties using the device and answer any questions.

INTERVENTION (Week 2 - 10) - AT THE HOMES OF THE PARTICIPANTS
Devices: Participants will be instructed to use the Sana PR every time they experience pain during the day (ad libitum). There will be no minimum or maximum number of uses.Participants will open the Sana Health application and will be prompted to answer the amount of pain they are feeling in the moment using the VAS on the Sana Health application. If it is the first time the participant is using the device for the day, they will also be prompted by the application to complete a VAS to report on how they slept the evening prior. Participants will then turn on the devices using the application. Participants will complete a 15-min cycle with the device. Participants may complete multiple, sequential uses of the devise without requiring them to interface with the application. Participants will be prompted to answer the amount of pain they are feeling in the moment after using the VAS on the Sana Health application.

Participants will also be asked to use the Sana PR device every evening immediately prior to/accompanying falling asleep for the night. Participants will open the Sana Health application and will be prompted to answer the amount of pain they are feeling in the moment using the VAS on the Sana Health application. Participants will then be prompted as to what medication they took for their pain that day. The application will be populated with the medications participants reported at the first baseline visit. Participants will select from this list of medications. Participants will complete a 15 min cycle with the device.

Every two weeks during the 8-week intervention period participants will receive a message on their cellular devices via text message to complete the NPSI, PSQI, PHQ-9 and GAD-7. Participants will be sent compliance reminders to complete these questionnaires on their phones and on the tablet.
Safety monitoring: Participants will be instructed to contact the research team to report any AE over this period. Compliance will be monitored over the 8 week intervention period. A significant decrease in the compliance during (responding to less than 70% of the last 10 scheduled check-ins) of using the device the 8 week intervention will be considered an indication that a participant may need assistance. A research team member will call the participant to ensure that the reason of the drop in usage of the device is not due to an AE.

POST INTERVENTION FOLLOW UP (Week 10) - AT THE ARC OR VIA VIDEO CALL Participant Information will be collected including:
- Record of changes in medications
- Record of changes in pain management techniques participants typically used
- Documentation of the location of their pain on a body chart

Participants will then complete the following questionnaires:
- Neuropathic Pain Symptom Inventory (NPSI)
- Pittsburgh Sleep Quality Index (PSQI)
- Beck Depression Inventory (BDI)
- Patient health Questionnaire Type 9 for Depression (PHQ-9)
- General Anxiety Disorder 7-item questionnaire (GAD-7)
- World Health Organization Quality of Life Bref (WHOQOL-BREF) & World Health Organization Quality of Life Pain (WHOQOL-pain)
- Patient's Global Impression of Change (PGIC)
- Human Factors Questionnaire

- Responses to questions on ease of device use and the likelihood they would hypothetically continue using the devices in their daily life.

Devices: Participants will be asked to return the Sana PR mask at this visit. The application will stop working to control the device at the end of the 8-week intervention and will not let participants to continue using the Sana PR device.

Safety monitoring: Participants will be asked to report any AEs.

CONTINUED PAIN MONITORING BETWEEN FOLLOW UP VISITS (Week 10 – Week 14) - AT THE HOMES OF THE PARTICIPANTS

Participants will be asked to use the tablet with the Sana application daily, at night prior to going to sleep. Participants will be asked to complete a VAS of how they slept the night prior, a VAS of their amount of pain and asked to report the medications they used that day for pain management.

4 WEEK FOLLOW UP VISIT (WEEK 14) - AT THE ARC OR VIA VIDEO CALL Participant information will be collected including:
- Record of changes in medications
- Record of changes in pain management techniques participants typically used - Documentation of the location of their pain on a body chart
Participants will then complete the following questionnaires: - Neuropathic Pain Symptom Inventory (NPSI)
- Pittsburgh Sleep Quality Index (PSQI)
- Beck Depression Inventory (BDI)
- Patient health Questionnaire Type 9 for Depression (PHQ-9)
- General Anxiety Disorder 7-item questionnaire (GAD-7)
- World Health Organization Quality of Life Bref (WHOQOL-BREF) & World Health Organization Quality of Life Pain (WHOQOL-pain)
- Patient's Global Impression of Change (PGIC)
- Human Factors Questionnaire
- Responses to questions on ease of device use and the likelihood they would hypothetically continue using the devices in their daily life.

Devices: Participants will be asked to return the tablet with the Sana application at this visit
Safety monitoring; Participants will be asked to report any AEs.

Description of the Source Records that Will Be Used to Collect Data About Subjects
Self-reported

Description of Data that Will Be Collected Including Long-Term Follow-Up
- Age, gender, name and contact information (phone number(s) and email address).
- Current medications: the list of medications will be collected to add to each participant's Sana Health application. - A self-reported medical history
- Documentation of the location of their pain on a body chart
- Documentation of what pain management techniques participants typically use
- Neuropathic Pain Symptom Inventory (NPSI)
- Pittsburgh Sleep Quality Index (PSQI)
- Beck Depression Inventory (BDI)
- Patient health Questionnaire Type 9 for Depression (PHQ-9)
- General Anxiety Disorder 7-item questionnaire (GAD-7)

- World Health Organization Quality of Life BREF (WHOQOL-BREF) & World Health Organization Quality of Life Pain (WHOQOL-pain)
- Record of changes in medications
- Record of changes in pain management techniques participants typically used - Documentation of the location of their pain on a body chart
- Patient's Global Impression of Change (PGIC)
- Human Factors Questionnaire
- Responses to questions on ease of device use and the likelihood they would hypothetically continue using the devices in their daily life.

4. Subjects

Enrollment goal: 180 participants

Inclusion Criteria

- Confirmed clinical diagnosis of neuropathic pain
- Ages 18+
- Fluent in English
- Consistent medications for the last 4 weeks prior to the first baseline visit (week 0)

Exclusion Criteria

- Diagnosis of photosensitive epilepsy
- Ear or eye infection
- Vision impairments that affect perception of light in one or both eyes
- Deafness in one or both ears
- Psychiatric disorders (participants will not be excluded if they score 0-30 points on the BDI, or if participants self- report having anxiety)

5. Data Analysis plan

We will use mixed modelling to determine the effect of the intervention on reported chronic pain – our primary outcome variable. We will also use ANOVAs (or their non-parametric equivalents) to assess changes in all of our outcome measures; including pain scores, sleep scores, device usage statistics, medication usage, heart rate variability, blood pressure, and quality of life measures.

6. Safety Assessment

Participants will be monitored for possible AEs throughout the study according to the frequency of the data review below. Participants will be given the email and phone number of the research team to report AE and circumstance of events. Participants will be reminded during the familiarization session with the device, at the second baseline visit, to seek immediate medical attention should they experience an injury as a result of being in the study. This will also be reiterated to participants if they reach out to report an AE. Data from the Sana Health application will be used to track compliance. Significant decrease in the compliance during (responding to less than 70% of the last 10 scheduled check-ins) of using the device the 8 week intervention will be considered an indication that a participant may need assistance. A research team member will call the participant to ensure that the reason of the drop in usage of the device is not due to an AE. Any AEs that occurs will be reported to the IRB to see if risk/benefit ratio is still acceptable for each individual participant and for the continuation of the study as a whole.

7. Benefits

Although no benefits can be guaranteed, it is possible that subject will experience a reduction in amount of chronic pain that they typically experience.

While there is no guarantee that this study will be beneficial to society, we hope that this study will help lead to the development of a device that can help reduce chronic pain and provide individuals who experience chronic pain with an alternative solution for managing pain.

8. Payment and Remuneration

There are no expected costs for participants in this study. We will pay participants a maximal total of $150 for your time and effort. This amount will be pro-rated: they will receive $25 for each of the two baseline assessments, and $50 for each of the two follow-up assessments, which amounts to $150. This will be paid to them in the form of a check following their final assessment. Checks require some time to be prepared and will be given to them as available. Payment is dependent on them returning both the Sana PR and tablet devices.