Journal of Psychiatry and Cognitive Behaviour
Sant DW, et al. J Psychiatry Cogn Behav 8: 173.
www.doi.org/10.29011/2574-7762.000073
www.gavinpublishers.com

Research Article

Amelioration of Anxiety Associated with Opioid Withdrawal by Activation of Spinal Mechanoreceptors Via Novel Heterodyned Whole Body Vibration

David W Sant[1], Christina A Nelson[1], JoAnn Petrie[2], Jonathan D Blotter[2], J Brent Feland[2], Daniel Adams[3], Marc Burrows[3], Jordan T Yorgason[2], Nathan D Schilaty[4], Kim H Manwaring[5], Kyle B Bills[1], Scott C Steffensen[1,2,6]

[1]Noorda College of Osteopathic Medicine, Provo, UT USA
[2]Brigham Young University, Provo, UT, USA
[3]PhotoPharmics, Inc, American Fork, UT USA
[4]University of South Florida, Tampa, FL, USA
[5]Nemours Children's Hospital, Orlando, FL, USA
[6]Nova Southeastern University, Ft. Lauderdale, FL, USA

***Corresponding author:** Scott C. Steffensen, Noorda College of Osteopathic Medicine, Provo, UT USA, Brigham Young University, Provo, UT, USA., Nova Southeastern University, Ft. Lauderdale, FL, USA.

Citation: Sant DW, Nelson CA, Petrie J, Blotter JD, Feland JB,et al. (2024) Amelioration of Anxiety Associated with Opioid Withdrawal by Activation of Spinal Mechanoreceptors Via Novel Heterodyned Whole Body Vibration. J Psychiatry Cogn Behav 7: 173. DOI: https://doi.org/10.29011/2574-7762.000073

Received Date: 20 February, 2024; **Accepted Date:** 19 March, 2024; **Published Date:** 21 March, 2024

Abstract

Objectives: Opioid use disorder (OUD)-associated overdose deaths have reached epidemic proportions worldwide. An important driving force for relapse is anxiety associated with opioid withdrawal. We hypothesized that our new technology, termed heterodyned whole-body vibration (HWBV) would ameliorate anxiety associated with OUD. **Methods:**Using a randomized, placebo (sham)-controlled, double-blind study design in an NIH-sponsored Phase 1 trial, we evaluated 60 male and 26 female participants diagnosed with OUD and undergoing treatment at pain and rehabilitation clinics. We utilized the Hamilton Anxiety Scale (HAM-A) and a daily visual analog scale anxiety rating (1-10) to evaluate anxiety. Subjects were treated for 10 min 5X/week for 4 weeks with either sham vibration (no interferential beat or harmonics) or HWBV (beats and harmonics). The participants also completed a neuropsychological test battery at intake and discharge. **Results:** In OUD subjects with moderate anxiety, there was a significant improvement in daily anxiety scores in the HWBV group compared to the sham treatment group ($p=3.41 \times 10^{-7}$). HAM-A scores in OUD participants at intake showed moderate levels of anxiety in OUD participants (HWBV group: 15.9 ± 1.6; Sham group: 17.8 ± 1.6) and progressively improved in both groups at discharge, but improvement was greater in the HWBV group ($p=1.37 \times 10^{-3}$). Furthermore, three indices of neuropsychological testing (mental rotations, spatial planning, and response inhibition) were significantly improved by HWBV treatment. **Conclusions:** These findings support HWBV as a novel, non-invasive, non-pharmacological treatment for anxiety associated with OUD.

Keywords: Substance Use Disorder (SUD); Opioid Use Disorder (OUD); Spinal Mechanoreceptor Activation from Vibration Motors Implanted Adjacent to the Laminae of the Cervical Vertebrae at C7-T1 (MStim); Whole-Body Vibration (WBV): Heterodyned WBV (HWBV); Hamilton Anxiety Scale A (HAM-A); Dopamine (DA); Opioid Receptors (ORs).

Introduction

Background and Significance

Substance use disorders (SUDs) and addictions are recognized as complex, chronically relapsing disorders of brain function and cognitive processing [1-4]. Ongoing research indicates that these neurobiological disorders often begin with recreational use that deteriorates into compulsive and self-destructive drug-seeking behaviors despite intentional and repeated efforts by the individual to discontinue use [1-3-5]. Opioid use disorder (OUD) is a rising problem in the United States and around the globe, with pain and anxiety being major factors for initial drug seeking and relapse [9-11]. Nearly 3 million Americans have an OUD, and less than 20% are estimated to receive treatment [12]. The estimated economic cost to the US in 2016 was $78.5 billion [13]. Over the past decade, OUD has reached epidemic proportions, in part due to inappropriate use of prescription opioid pain killers [14]. In August 2017, OUD was identified as a public health emergency following national and state commission recommendations [15]. The success rate of OUD treatments has not significantly changed over the last 100 years [5-7]. The current Food and Drug Administration (FDA)-approved pharmacological treatments for OUD include the slowly acting opioid receptor (OR) agonist methadone, the mixed OR agonist/antagonist buprenorphine (e.g., common brands: Buprenex, Subutex, Suboxone), the μ-OR (MOR) antagonist naltrexone (e.g., common brands: Revia and Vivitrol), institutionalized care, and/or various counseling and behavioral therapies.

Pre-clinical Studies and Proof of Concept

The use of mechanoreceptor (MR)-based technologies in the treatment of drug-abuse disorders is a largely unexplored field. Indeed, the role of MRs, other than as canonical mediators of somato-sensation, has only become relevant in recent years. Conventional therapies like whole body vibration (WBV), which are predicated on MR activation, have been shown to positively impact power and strength [16], flexibility [17,18], balance [19], bone metabolism [20], hormone release [21], and falls in the elderly [22]. Recent reports have included evidence of increased cortical excitability [23], increased motor evoked potentials [24], and evidence demonstrating brain changes in response to WBV as measured with fMRI, electroencephalographic activity, heart rate variability (HRV), and electro-cortical evoked potentials [23,25-27].

There is evidence suggesting that some of the benefits ascribed to acupuncture and chiropractic spinal manipulation are mediated through selective activation of specific MRs via non-canonical somatosensory neuronal pathways. Accordingly, we demonstrated in rodents that cutaneous MR activation *via* electroacupuncture at acupoint HT7 produced a biphasic modulation of GABA neurons in the ventral tegmental area (VTA) characterized by transient enhancement of firing rate followed by inhibition (50%) of firing rate and subsequent recovery in 5 minutes [28], which was blocked by the non-selective OR antagonist naloxone and the selective δ-OR (DOR) antagonist naltrindole, suggesting a role for endogenous opioids. We have more recently demonstrated [29,30] that brief (60-120 sec), low frequency (45-80 Hz), but not higher frequency (115 Hz), spinal mechanoreceptor activation from vibration motors implanted adjacent to the laminae of the cervical vertebrae at C7-T1 (termed "MStim") inhibited the firing rate of VTA GABA neurons (52.8% baseline for 450 sec), while increasing the firing rate of VTA DA neurons (248% baseline for 500 sec), that was blocked by systemic naloxone and local administration of both the DOR antagonist naltrindole or the muscarinic antagonist scopolamine in the NAc, further suggesting a role for endogenous opioid release and modulation of accumbal cholinergic interneurons (CINs).

Perhaps of most translational relevance is that the effects of spinal MStim persisted considerably beyond the duration of the stimulus [30]; mainly, DA release in the NAc was enhanced for more than 1 hr after a brief 1 min 80 Hz stimulation of the C7-T1 laminae, despite the fact that VTA GABA neurons were only inhibited, and DA neurons only excited, for 5-10 min by the 1 min stimulation. Neurons in the NAc, but not the VTA, evinced cFos activation by MStim and MStim-induced DOR expression and translocation to the plasma membrane in presumed NAc CINs 1 hr after the stimulation. Stimulation to the cervical spine produces a much more robust effect than stimulation or activation of cutaneous MRs, likely due to the disproportionately large number of MRs in the cervical spine. We found that WBV positively influenced affective state due to its induction of DA release. More recently, we sought to determine if WBV, at the same frequencies as MStim, might have behavioral effects and ameliorate neuronal, neurochemical, and behavioral indices of ethanol (EtOH) and opioid dependence. WBV administered for 15 min, 5 min after EtOH injection (twice-daily at 2.5 g/kg) at 80 Hz prevented the enhanced baseline excitability of VTA GABA neurons, tolerance to acute EtOH inhibition of VTA GABA neuron firing rate, reduction of EtOH enhancement of DA release, behavioral indices of EtOH withdrawal, as well as anxiety, associated with withdrawal from chronic EtOH exposure in rats [31]. More recently, we have reported a similar study in rodents withdrawing from chronic morphine. Mainly, WBV prevented molecular (i.e., DORs), neuronal (i.e., VTA GABA projects to the NAc), neurochemical

(i.e., DA release) and behavioral (i.e., anxiety) indices of morphine withdrawal [32]. Thus, a non-pharmacological intervention can prevent manifestations of EtOH and opioid dependence. We are unaware of any other treatment, pharmacological or otherwise, that blocks molecular, neuronal, neurochemical, and behavioral measures of EtOH dependence in rodents. Regardless, these studies provide compelling pre-clinical proof-of-concept evidence that MR activation by primary somatosensory fibers with specific MStim/WBV parameters modulates midbrain neurons and DA transmission in the mesolimbic reward system in rodents via endogenous opioid release and that MR activation by WBV at specific frequencies is an adequate stimulus to ameliorate neuronal, neurochemical, and behavioral indices of EtOH and opioid withdrawal in animal models.

Translational Clinical Studies, Rationale, and Hypotheses

Informed by these pre-clinical studies in rodents, it seemed logical that enhancing DA release non-pharmacologically via spinal MR stimulation might be a potential treatment for ameliorating anxiety in OUD. Thus, the primary measure in this study was anxiety associated with opioid dependence. We hypothesized that HWBV would be effective in reducing anxiety associated with OUD compared to sham stimulation.

Materials and Methods

Participants

Based on a pilot study with generalized anxiety in non-OUD subjects, which was used as preliminary data for the NIH-sponsored randomized, placebo (sham)-controlled, double-blind clinical trial, we proposed to recruit 60 OUD subjects (30 men and 30 women) between the ages of 20-60 who were currently going through withdra walfrom OUD. Subject numbers were projected based on the preliminary study in non-OUD subjects, as well as a power analysis through our non-OUD studies assuming a high Power of 0.8 and a conservative Alpha of 0.05 and including a potential drop-out rate of approximately 25%. A total of 86 male and female participants completed at least part of the study (Supplemental Table 1), more than the projected number of participants. All OUD individuals were recruited with the approval and help of the trained and licensed staff of evidenced-based, high-intensity pain clinics, and residential and detoxification treatment facilities in Utah, USA, adhering to 42 CFR Part 2 law [33]. These treatment centers were state-licensed detoxification and addiction treatment center for treatment of persons with or without co-occurring mental health disorders, comorbid with SUDs, and addiction, including OUD, and required to meet the very stringent confidentiality and established regulations of the 1996 Health Insurance Portability and Accountability Act (HIPAA) [33]. These treatment programs and facilities provided SUD care according to the current published American Society of Addiction Medicine (ASAM) Patient Placement Criteria, with diagnoses of OUD based on the American Psychiatric Association's (APA) Diagnostic Statistical Manual (DSM)-IV-TR development criteria [1,2]. However, it was understood that for the purposes of this study, the OUD cohort were all in various stages of withdrawal from their OUD, as short as 2-weeks from last opioid use but for no longer than 4 weeks out at the time of intake. Most were at some stage of opioid replacement therapy (e.g., Suboxone). Participants from both cohorts were matched as closely as possible for age and gender [34] ranging in age from 20-61 years once pre-screening self-report questionnaires were completed by all participants to ensure basic good health.

Ethical Considerations

Studies with OUD were approved by a multi-site ADVARRA IRB (Pro00050259). Confidentiality and compliance met HIPAA requirements for research data collected, all clinical and research personnel were trained in confidentiality protocols and maintained the required Collaborative Institutional Training Initiative (CITI) certifications [35]. All those involved in the research project signed confidentiality agreements. Signed consent forms were received from all participants prior to any testing, then immediately given research identification numbers. All electronic data were stripped of any unique identifiers (e.g., name, date of birth) and stored in a secure electronic database. Only de-identified data were entered into the multi-lab computer database or EEG console-all data entries were done by two raters for accuracy. All other data and materials collected were secured, including all hard copies of questionnaires and consent forms. These were only marked with participant numbers that were unique to the study.

Treatment Sessions

The Hamilton Anxiety Rating Scale (HAM-A) was administered to all non-OUD subjects at intake and at the end of each week of treatment. The HAM-A demonstrates acceptable levels of inter-rater reliability and consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Subjects underwent treatment at the same time each day to account for circadian rhythm and the caregivers reported if there has been a change in timing of any secondary medications (if applicable), recidivism, relapse, absenteeism, etc., during the treatment protocol. All qualified OUD subjects were randomized to 1 of 2 independent treatment groups: Sham or HWBV. Subjects underwent 10 min of treatment on each weekday at their respective treatment center for a period of 4 weeks. Only one chair system was available at each treatment center, but the stimulation parameters were different for HWBV (beat and harmonics) *vs* sham (no beat nor harmonics) treatment based on their group randomization and blinded to both subject and operator. The same protocol was followed for the

OUD participants as above with the addition of the Clinical Opiate Withdrawal Scale (COWS) and neuropsychiatric testing, which were completed at intake and at discharge. Neuropsychiatric testing was performed using the established Creyos protocol (https://creyos.com, Toronto, ON, Canada). Percentile scores from Creyos are given as percentile scores, accounting for age and sex.

Inclusion and Exclusion Criteria

Eligibility for each volunteer participant was initially established through a brief in-person interview with either a licensed staff member and/or therapist at the recruiting treatment center or by a trained research assistant referring to an already established and approved Pre-Screening Checklist developed for the study. Inclusion criteria for OUD subjects were: official opioid addiction diagnosis; current daily craving for opioids; absence of opioid use in past 2 weeks or longer than 4 weeks out; willingness to indicate drug use history; no prior history of severe brain injury; no history of seizure; age above 18; and no history of fainting. Exclusion criteria were based, in part, on inclusion criteria but also included: refusal to give informed consent; refusing treatment; relapse to opioid use; pregnancy; and known ethanol or drug use during treatment. There was no exclusion based on sex, race, or ethnicity. Participants with OUD had been diagnosed following the DSM-IV-TR manual, were detoxified from all substances including opioids, but still experiencing daily craving for drugs. Our study procedures required approximately 3 hours at the clinic completing neuropsychological testing--all participants agreed to give of that time in one session. Each participant agreed to keep proceedings confidential.

Protections Against Risk

Risks were minimal for involvement in this study, as the stimulus was limited to mechanical vibrations from the seat of the chair and those associated with safely getting in and out of a chair. Subjects were assisted by staff members while sitting down and getting up out of the vibrating chair. The danger of over excitation due to chair vibration was minimal because the vibration transducers were tested and shown to be incapable of providing a harmful vibration response. Actuators had automatic thermal shutdown built in. Otherwise, there was no risk of over-heating with use during the short 10 min sessions. We did not observe any untoward psychological, social, cultural, financial, or legal risks associated with this trial. Subjects were able to withdraw from the study at any time without consequence. Subjects were advised a priori of the potential for discomfort and were asked to immediately make the clinician aware of any discomfort or pain experienced during the assessment. Subjects were informed that they could simply stand up out of the chair if they felt any pain or discomfort. All assessments were performed under the supervision of facility trained clinicians.

Data and Safety Monitoring Plan

Volunteer subjects were asked to sit in a vibrating chair and subjected to either HWBV or sham stimulation as described above. This was a low amplitude vibration (displacement < 2 mm) that was intended to be comfortable to the subject while stimulating various MRs. De-identification was as described previously. All data, as well as the mapping between identifiers and subjects were kept on secure, password-protected computers accessible only by authorized investigators on this project. The facility trained staff ensured that all survey results and other confidential data were securely recorded without identification. All investigators were required to undergo human subjects research training and certification through the Collaborative Institutional Training Initiative (CITI training) and provide a copy of their training certificate to BYU's IRB for non-OUD subjects and ADVARRA multi-site IRB for OUD subjects. Facility trained staff were with each subject during all phases of testing. Plans were in place that if any adverse events occurred, the trained staff were responsible for reporting the adverse event to their supervisor and the trained staff working with the study. The facility supervisor was instructed to follow the facility guidelines for reporting adverse events. No adverse events occurred in this study.

Statistical Analyses

For each measure, subjects within each group were analyzed using paired t-tests. Comparison of subjects between groups at intake were analyzed using student's t-tests. Comparison of subjects between groups at timepoints aside from the initial intake were analyzed using linear mixed models (LMM), using intake value and age as covariates. Overall comparison between groups was performed using LMM with intake value, age, and week of measurement as covariates. Measures repeated at multiple time points and neuropsychiatric testing (which consisted of twelve independent measures) were corrected using Benjamini-Hochberg correction (false discovery rate, FDR) before determining significance.

Results

Heterodyned Whole Body Vibration (HWBV)

Informed by pre-clinical studies lending promise to the translational potential of enhancing DA *via* endogenous opioids by selective activation of spinal MRs at relevant frequencies, we constructed a novel chair-based HWBV system that propagates traveling waves up and down the entire human spinal column from a sitting position with the ability to regionally localize and recruit spinal MRs (Figure 1A-D). The system was designed to optimally transfer the heterodyned vibration beneath the split-chair seat throughout the spine and to induce relevant harmonics from 40-80 Hz that emulate those found in pre-clinical studies summarized above. Using a scanning laser Doppler vibrometer to measure the

vibration, we demonstrated our ability to induce a traveling wave in the human torso (Figure 1E-F) with interferential vibration from the actuators beneath each isolated seat half. We found that interferential frequencies from dual actuators at 24-26 Hz with a split-seat design induced a traveling wave at the beat frequency and induced 40-80 Hz harmonics at the vertex of the head (Figure 1G-H). Vibration without interferential vibration produced no beat, no traveling waves, and no harmonics at the head, and was used as the sham treatment condition.

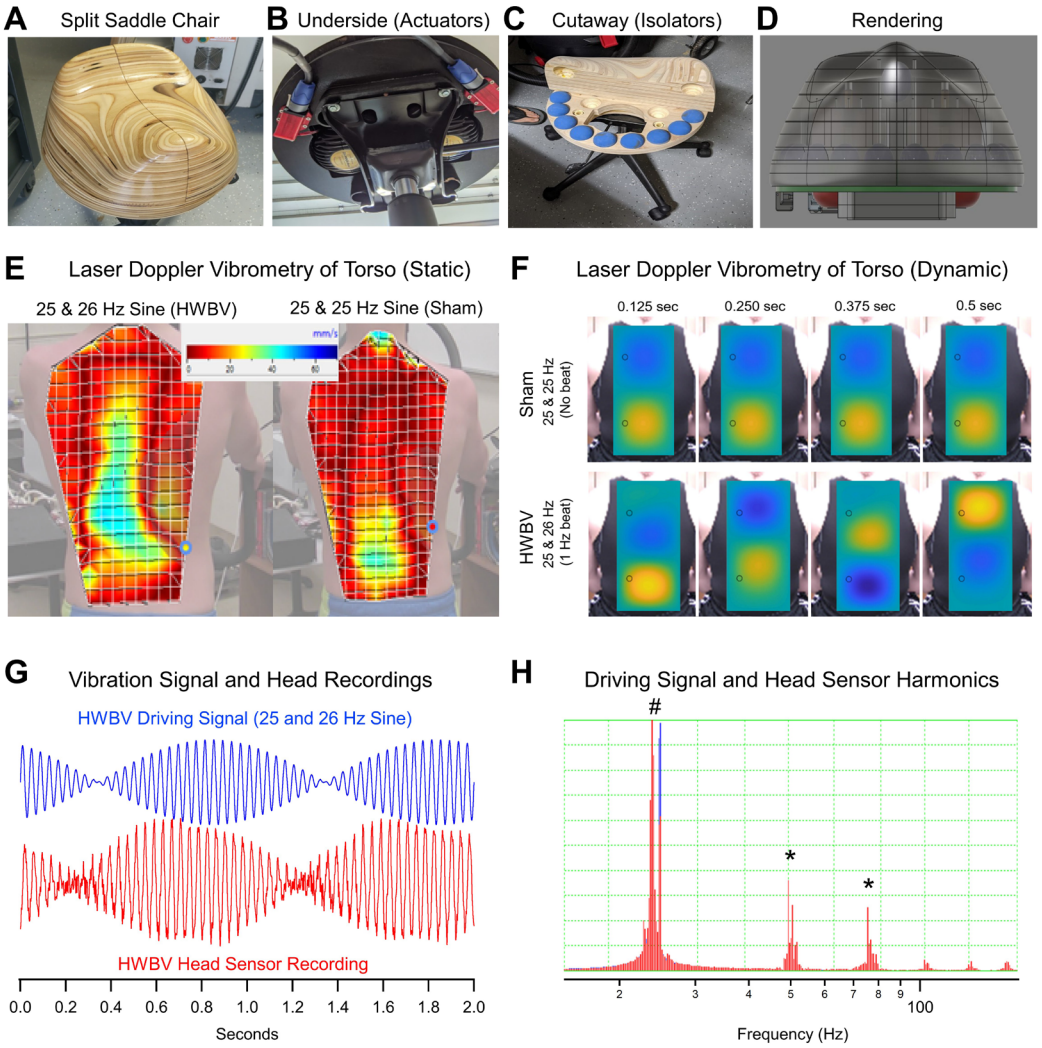

Figure 1: Heterodyned whole-body vibration (HWBV): (A-C) Images of the split saddle chair used in the study to produce HWBV showing actuators and isolators; (D) Design rendering of split saddle chair; (E) Laser doppler vibrometer measurements from the back torso of a subject sitting on a split-chair excited by independent low frequency effect (LFE) actuators beneath the seat at 25 and 26 Hz (left) and 25 and 25 Hz (right) captured during a 1 Hz beat (static response). Note the snapshot in time of the traveling wave up the spinal column with the 25 and 26 Hz sine stimulus; (F) Laser doppler vibrometer measurements from the back torso of a subject sitting on a split-chair over time (dynamic response). The top row shows the steady state response obtained by independent actuator excitation without an interferential frequency (25 and 25 Hz) at 4 sequential time frames (0-0.5 sec), and the bottom row shows the response that is obtained using interferential frequency (25 and 26 Hz) demonstrating the traveling wave that is foundational to HWBV; (G) The driving signal to the actuators from the sine wave generator is shown (top) combined at 25 and 26 Hz. Note the beat frequency of 1 Hz. The signal from a piezoelectric sensor positioned at the vertex of the head evinced vibration patterns with 25 and 26 Hz sine waveforms to the two halves of the chair; (H) Spectrograph of the driving and head sensor signals. Note the fundamental frequency of the driving signals (hashtag at 25 and 26 Hz; blue and red) and the head sensor (red) with harmonics at the vertex at approximately 50 and 80 Hz (asterisks), consistent with the MStim frequencies used in pre-clinical studies in rodents to modify mesolimbic DA transmission.

HWBV Reduced Anxiety Associated With OUD

Informed by the outcome of amelioration of generalized anxiety in non-OUD participants with HWBV, we were awarded an NIH Phase I grant to conduct a randomized, placebo (sham)-controlled, double-blind Phase 1 clinical trial in 60 subjects with OUD (MPIs Steffensen and Adams; DA053083). The study ran from 2020-2022, one year longer than the expected timeline due to the COVID-19 pandemic. The Phase I clinical trial primary aim was to evaluate the efficacy of HWBV to ameliorate anxiety associated with OUD. We used the same system and parameters shown effective in reducing generalized anxiety in a pilot study in non-OUD student subjects. Although there was considerable participant attrition (10 participants were unable to complete the study and 33 voluntarily withdrew), in part due to the COVID-19 pandemic, but also due to relapse, dismissal from the program, change in treatments, pregnancy, etc., we were able to evaluate 86 OUD male and female participants, 26 more than we proposed initially. Attrition rates were significantly higher in the sham group than the HWBV group ($p=2.81\times10^{-4}$).

HWBV Reduced Symptoms of Dependence

Surprisingly, COWS scores were relatively low at intake, likely due to intakes occurring a minimum of two weeks following last opioid use, and ongoing opioid replacement therapy with *Suboxone*, etc... Although COWS scores were low at intake and there was attrition, especially among subjects in the sham treatment group, HWBV significantly reduced COWS scores across the 4 weeks of the trial compared to intake baseline ($p=0.011$) and between groups ($p=0.020$, Supplemental Table 2).

HWBV Reduced Anxiety Associated With OUD

At intake, anxiety was measured on a scale from 1-10 using a visual analog scale. The average reported value for the sham group was 3.9 ± 0.3 and the average reported value for the HWBV group was 3.8 ± 0.3 ($p=0.70$). HWBV treatment significantly reduced daily anxiety scores in OUD subjects compared to intake baseline and compared between groups ($p=3.41\times10^{-7}$) (Figure 2A, Supplemental Table 3). HAM-A scores at intake evinced moderate anxiety, with averages of 17.8 ± 1.6 in the sham group and 15.2 ±1.6 in the HWBV group ($p=0.27$). Perhaps most importantly, HWBV reduced HAM-A anxiety scores in OUD subjects compared to intake baseline and compared between groups ($p=1.37\times10^{-3}$, Figure 2B, Supplemental Table 4).

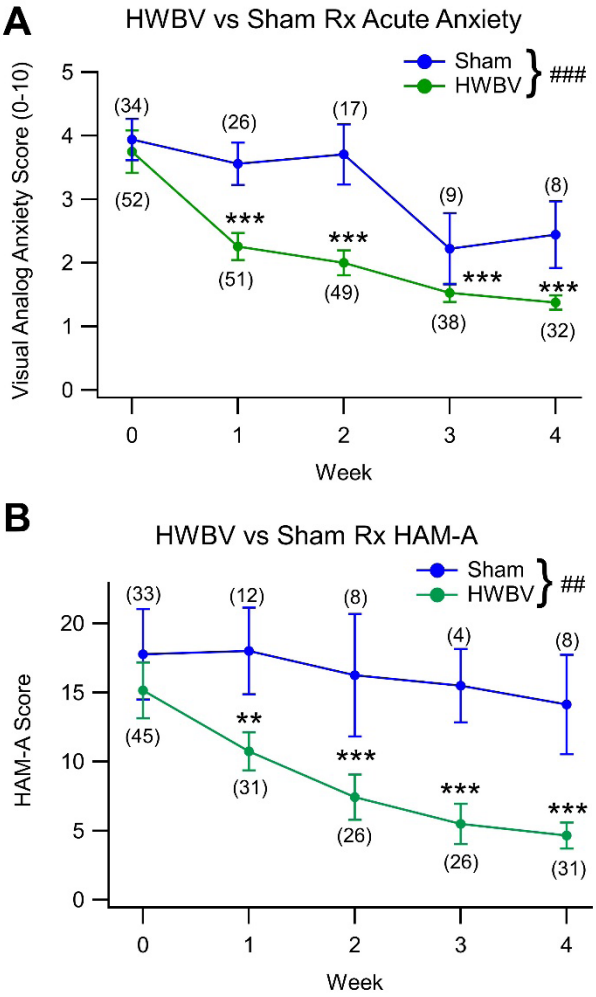

Figure 2: Amelioration of anxiety associated with OUD by heterodyned whole-body vibration; (A) HWBV treatment progressively reduced daily anxiety scores in OUD subjects based on a simple daily VAS 0-10 scale compared to intake baseline and compared to sham controls; (B) HWBV significantly reduced HAM-A scores in OUD subjects starting at the first week of treatment and progressively increasing after 4 wk compared to intake baseline and compared with sham controls. Asterisks *,**,*** represent significance levels FDR<0.05, 0.01, and 0.001, respectively, for comparisons to intake measures. Hashtags #, ##, ### represent significance levels p<0.05, 0.01, and 0.001 for comparisons between groups. Numbers in parentheses represent n values.

HWBV Improved Some Cognitive Outcomes Associated with OUD

Along with evaluation of anxiety in OUD subjects in the Phase I clinical trial, we evaluated select measures of cognitive performance between intake baseline and discharge at 4 weeks. Compared to sham treatment, HWBV improved performance (pre- vs post-Rx normalized scores) in some tests including mental rotations (FDR = 0.047), spatial planning (FDR = 0.018), and response inhibition (FDR = 0.018) (Figure 3, Supplemental Table 5).

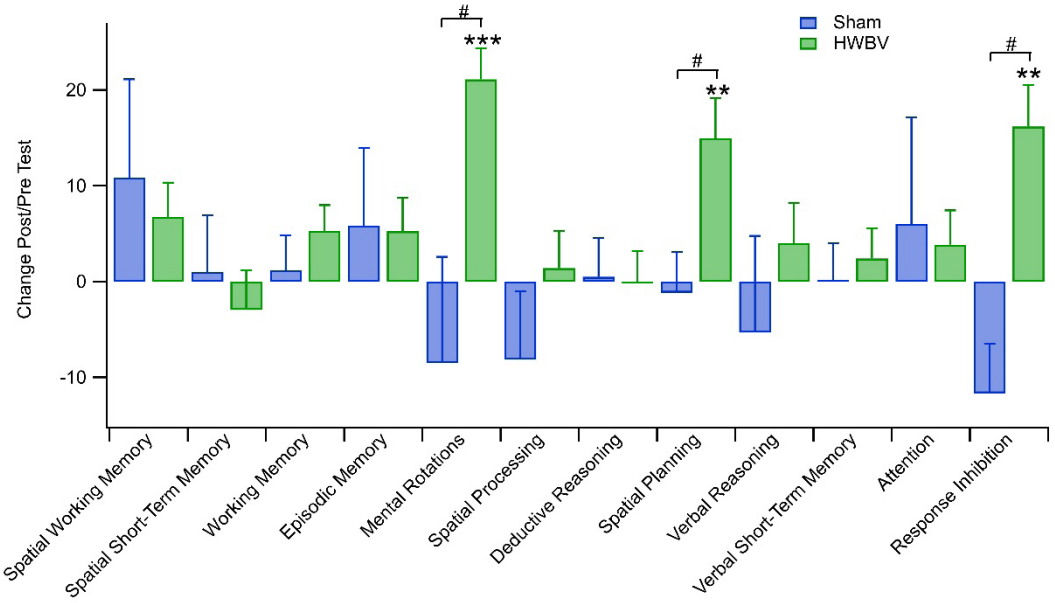

Figure 3: Improvement in select cognitive measures with heterodyned whole-body vibration. Neuropsychology testing demonstrated that OUD subjects treated with HWBV had higher cognitive performance pre- *vs* post-Rx normalized scores in some tests including mental rotations, spatial planning, and response inhibition: Asterisks **,*** represent significance levels FDR<0.01 and 0.001, respectively, for comparisons to intake baseline measures. HWBV treatment markedly improved these measures compared to sham controls. Hashtags #,##,### represent significance levels FDR<0.05, 0.01, and 0.001 for comparisons between HWBV and sham treatment groups.

Discussion

We conducted an NIH-sponsored Phase I clinical trial in non-OUD subjects and subjects with OUD to determine the efficacy of HWBV to ameliorate anxiety. Informed by pre-clinical studies in rodents, we hypothesized that 40-80 Hz spinal stimulation would modulate DA release and ameliorate anxiety and hedonic drive. We speculated that MRs have similar activation energies and frequency response in rodents as in humans. We chose a split-chair device design with actuators positioned orthogonally to the seat to optimize displacement. It was only when we employed interferential ("beat") frequencies at the two isolated actuators positioned at the ischial tuberosities that we observed a pronounced traveling waveform up the spinal column at the beat frequency and harmonics from 40-80 Hz at the head. We speculate that these frequencies are multiples of the fundamental driving frequencies and generated by the body load with resonance at the harmonic frequencies and carried optimally by the beat wave up the spinal column, suggesting gain of MR activation up the spinal column with the split-chair design. Importantly, harmonics evident at 40-80 Hz at the head became the criterion (i.e., the "adequate stimulus") for determination of the parameters for HWBV used in non-OUD participants in the pilot study and in OUD participants in the clinical trial.

Informed by this success in non-OUD participants and with funding from NIH, we commenced a Phase I clinical trial in OUD participants. Although all the subjects in the OUD trial received an initial diagnosis of OUD, COWS scores at intake in our 86 subjects were relatively low at intake due to abstinence from opioids for two-weeks, indicating a mild-moderate state of dependence. Regardless, HWBV reduced total COWS scores in comparison to sham treatment (no beat, no harmonics). Importantly, HWBV also reduced daily acute anxiety scores and weekly HAM-A scores in individuals with OUD compared to baseline intake and compared to sham

controls. Furthermore, 3 indices of neuropsychological testing were significantly improved by HWBV at discharge compared to intake. These studies provide proof-of-concept evidence to support HWBV as a novel, non-invasive, non-pharmacological treatment for generalized anxiety and anxiety associated with OUD. These results were obtained despite ongoing OUD treatment at the pain and rehabilitation clinics. Interestingly, three measures of cognitive performance were improved by HWBV including: mental rotations; spatial planning; and response inhibition. As our clinical trial did not assess brain DA levels in humans, which is problematical at best, we can only speculate how the DA enhancement seen in rodents might extrapolate to humans. Dopamine levels have been implicated in all three of these neurocognitive phenotypes. Thus, enhanced DA levels by HWBV treatment might account for the enhancement observed with these measures.

Conclusions

These findings support HWBV as a novel, non-invasive, non-pharmacological treatment for anxiety associated with OUD. Persons suffering from OUD continue their cycle of abuse, in part, because of maladapted or depleted DA levels, with its accompanying dysphoria, as well as anxiety and stress mediated by the extended amygdala accompanying the 'withdrawal/negative affect' phase of the addiction cycle. Based on pre-clinical studies, we speculate that HWBV reduces anxiety associated with withdrawal from OUD by enhancing baseline DA levels in the mesocorticolimbic system and reducing the driving force for relapse.

Acknowledgments

We would like to thank the men and women struggling with OUD who participated in the clinical trial.

Funding

This work was funded by NIH grants DA053083 to Dan Adams and Scott Steffensen. Clinical Trials.gov registration number: NCT05056753

Declaration of conflicting Interests

The authors declare that there are no conflicts of interest regarding the publication of this paper. All authors have contributed to the preparation of the manuscript and have read and approved the submitted manuscript. All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors and are in agreement with the manuscript.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV). American Psychiatric Association; 1994:886.
2. American Psychiatric Association (2012) DSM-5 Development: Substance Related Disorders.
3. American Psychiatric Association, ed. Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5). Fifth ed. American Psychiatric Publishing; 2013.
4. Grant JE, Chamberlain SR (2016) Expanding the definition of addiction: DSM-5 *vs.* ICD-11. CNS spectrums. CNS Spectr 21: 300-303.
5. DiFranza JR (2008) Hooked from the first cigarette. Sci Am 298: 82-87.
6. United Nations Office on Drugs and Crime (UNODC). World Drug Report 2020. 2020:52. #2 Drug Use and Health Consequences. Sales No. E.20.XI.6. June 20, 2020. Accessed Nov 14, 2020.
7. Bartram A, Eliott J, Crabb S (2017) 'Why can't I just not drink?' A qualitative study of adults' social experiences of stopping or reducing alcohol consumption. Drug Alcohol Rev 36: 449-455.
8. Hoffman J, Froemke S, eds. Addiction: Why can't they just stop? First ed. Rodale Books; 2007.
9. Varghese SP, Montalvo-Ortiz JL, Csernansky JG, Eiger IR, Herrold AA, et al. (2015) Early Life Stress as a Risk Factor for Substance use Disorders: Indian J Psychol Med 37: 36-41.
10. Koob GF (2008) A role for brain stress systems in addiction. Neuron 59: 11-34.
11. Sinha R (2008) Chronic stress, drug use, and vulnerability to addiction. Ann NY Acad Sci 1141: 105-130.
12. Abuse S (2009) Mental Health Services Administratio Results from the 2008 national survey on drug use and health: National findings. 2010;
13. Florence CS, Zhou C, Luo F, Xu L (2013) The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. Med Care 54: 901-906.
14. Passik SD (2009) Issues in long-term opioid therapy: Unmet needs, risks, and solutions. Case ReportsReview. Mayo Clinic Proceedings Mayo Clinic 84: 593-601.
15. House W (2017) Report of the President's Commission on Combating Drug Addiction and the Opioid Crisis.
16. Bosco C, Cardinale M, Tsarpela O (1999) Influence of vibration on mechanical power and electromyogram activity in human arm flexor muscles. Eur J Appl Physiol Occup Physiol 79: 306-11.
17. Feland JB, Hawks M, Hopkins JT, Hunter I, Johnson AW, et al. (2010) Whole body vibration as an adjunct to static stretching. Int J Sports Med 31: 584-589.
18. Houston MN, Hodson VE, Adams KK, Hoch JM (2015) The effectiveness of whole-body-vibration training in improving hamstring flexibility in physically active adults. J Sport Rehabil 24: 77-82.
19. Tseng SY, Hsu PS, Lai CL, Liao WC, Lee MC, et al. (2016) Effect of Two Frequencies of Whole-Body Vibration Training on Balance and Flexibility of the Elderly: A Randomized Controlled Trial. Am J Phys Med Rehabil 95: 730-737.
20. Dionello CF, Sa-Caputo D, Pereira HV, Gonçalves SRC, Maiworm AI, et al. (2016) Effects of whole body vibration exercises on bone mineral density of women with postmenopausal osteoporosis without medications: novel findings and literature review. J Musculoskelet Neuronal Interact 16: 193-203.
21. Paineiras-Domingos LL, Sa-Caputo DDC, Moreira-Marconi E, Morel SD, Fontoura Dionello DC, Tamini S, et al. (2017) Can whole body

vibration exercises affect growth hormone concentration? A systematic review. Growth Factors 35:189-200.

22. Jepsen DB, Thomsen K, Hansen S, Jorgensen NR, Masud T, et al. (2017) Effect of whole-body vibration exercise in preventing falls and fractures: a systematic review and meta-analysis. BMJ Open 7: e018342.
23. Krause A, Gollhofer A, Freyler K, Jablonka L, Ritzmann R (2016) Acute corticospinal and spinal modulation after whole body vibration. J Musculoskelet Neuronal Interact 16: 327-338.
24. Mileva KN, Bowtell JL, Kossev AR (2009) Effects of low-frequency whole-body vibration on motor-evoked potentials in healthy men. Exp Physiol 94: 103-116.
25. Zhang N, Fard M, Bhuiyan MHU, Verhagen D, Azari MF, et al. (2018) The Effects of Physical Vibration on Heart Rate Variability as a Measure of Drowsiness. Ergonomics 61: 1259-1272.
26. Kaut O, Becker B, Schneider C, Zhou F, Fliessbach K, et al. (2016) Stochastic resonance therapy induces increased movement related caudate nucleus activity. J Rehabil Med 48: 815-818.
27. Satou Y, Ishitake T, Ando H, Nagatomi K, Hoshiko M, et al. (2009) Effect of short-term exposure to whole body vibration in humans: relationship between wakefulness level and vibration frequencies. Kurume Med J 56:17-23.
28. Yang CH, Yoon SS, Hansen DM, Wilcox DJ, Blumell RB, et al. (2010) Acupuncture inhibits GABA neuron activity in the ventral tegmental area and reduces ethanol self-administration. Alcohol Clin Exp Res 34: 2137-2146.
29. Bills KB, Clarke T, Major GH, Jacobson CB, Blotter DJ, et al. (2019) Targeted Subcutaneous Vibration With Single-Neuron Electrophysiology As a Novel Method for Understanding the Central Effects of Peripheral Vibrational Therapy in a Rodent Model. Dose Response Jan-Mar 17: 1559325818825172.
30. Bills KB, Obray JD, Clarke T, Parsons M, Brundage J, et al. (2020) Mechanical stimulation of cervical vertebrae modulates the discharge activity of ventral tegmental area neurons and dopamine release in the nucleus accumbens. Brain Stimul 13: 403-411.
31. Bills KB, Otteson DZ, Jones GC, Brundage NJ, Baldwin KE, et al. (2022) Mechanical Stimulation Alters Chronic Ethanol-Induced Changes to VTA GABA Neurons, NAc DA Release and Measures of Withdrawal. Int J Mol Sci 23: 12630.
32. Jones GC, Small CA, Otteson DZ, Hafen WC, Breinholt TJ, et al. (2023) Whole-Body Vibration Prevents Neuronal, Neurochemical, and Behavioral Effects of Morphine Withdrawal in a Rat Model. International journal of molecular sciences 24: 14147.
33. Fact Sheet: SAMHSA 42 CFR Part 2 Revised Rule. HHS.gov.
34. Hedden T, Gabrieli JD (2004) Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci 5: 87-96.
35. CITI Program. The Collaborative Institutional Training Initiative (CITI Program).

	Count		
Recruited	110		
Declined to participate	12		
Did not meet inclusion criteria	1		
Became pregnant (excluded)	1		
Multiple strokes (excluded)	1		
Declined to receive treatment	9		
Remaining	86		
Sham Group (n = 34)	**Count**	**Percent**	**Median (Min, Max)**
Age			**36 (20, 57)**
Male	27	79.4%	
Female	7	20.6%	
Completed Study	8	23.5%	
Unable to Continue	5	14.7%	
Voluntarily Withdrew	21	61.8%	
HWBV Group (n = 52)	**Count**	**Percent**	**Median (Min, Max)**
Age			**33 (20, 61)**
Male	33	63.5%	
Female	19	36.5%	
Completed Study	35	67.3%	
Unable to Continue	5	9.6%	
Voluntarily Withdrew	12	23.1%	

Supplemental Table 1: Descriptive statistics of the 110 individuals recruited for the study, 86 met the inclusion criteria and did not meet any exclusion criteria.

	Mean (± S.E.M.)		**Comparison Within Subjects**		**Comparison Between Subjects**
	Sham	HWBV	Sham	HWBV	
Intake	6.8 (0.9)	5.6 (1.0)	-	-	0.38
Discharge	6.6 (1.4)	2.1 (0.6)	0.54	0.011 *	0.02 *

Supplemental Table 2: Clinical Opiate Withdraw Scale (COWS) Statistical Results; Comparison within subjects represent p-values from paired t-tests. Comparison between subjects at intake is a p-value from student's t-test, and at discharge is a p-value from linear mixed models, using intake value and age as covariates; * $p<0.05$.

	Mean (± S.E.M.)		Comparison Within Subjects		Comparison Between Subjects
	Sham	HWBV	Sham	HWBV	
Intake	3.9 (0.3)	3.8 (0.3)	-	-	0.70
Week 1	3.6 (0.3)	2.3 (0.2)	0.52	5.8×10^{-7} ***	2.5×10^{-4} ***
Week 2	3.7 (0.5)	2.0 (0.2)	0.85	4.2×10^{-7} ***	1.1×10^{-4} ***
Week 3	2.2 (0.6)	1.5 (0.1)	0.47	4.0×10^{-6} ***	0.03 *
Week 4	2.4 (0.5)	1.4 (0.1)	0.47	1.2×10^{-6} ***	4.6×10^{-3} **

Supplemental Table 3: Median Daily Anxiety Visual Analog Scale (VAS) Statistical Results; Comparisons within subjects represent Benjamini-Hochberg false discovery rates (FDRs) from paired t-tests. Comparison between subjects at intake is from student's t-test. Remaining between subjects comparisons represent FDRs from linear mixed models, using intake value and age as covariates. Overall linear mixed models group p-value = 3.41×10^{-7}. * FDR<0.05, ** FDR<0.01, *** FDR<0.001.

	Mean (± S.E.M.)		Comparison Within Subjects		Comparison Between Subjects
	Sham	HWBV	Sham	HWBV	
Intake	17.8 (1.6)	15.2 (1.6)	-	-	0.27
Week 1	18.0 (2.9)	10.7 (1.2)	0.06	5.6×10^{-3} **	7.9×10^{-4} ***
Week 2	16.3 (4.4)	7.4 (1.4)	9.3×10^{-3} **	1.9×10^{-5} ***	1.5×10^{-3} **
Week 3	15.5 (2.7)	5.5 (1.2)	0.06	1.9×10^{-5} ***	4.5×10^{-4} ***
Week 4	14.1 (3.7)	4.4 (0.8)	0.111	2.4×10^{-6} ***	5.6×10^{-10} ***

Supplemental Table 4: Hamilton A Statistical Results**;** Comparison within subjects represent Benjamini-Hochberg false discovery rates (FDRs) from paired t-tests. Comparison between subjects at intake is from student's t-test. Remaining between subjects comparisons represent FDRs from linear mixed models, using intake value and age as covariates. Overall linear mixed models group p-value = 1.37×10^{-3}. * FDR<0.05, ** FDR<0.01, *** FDR<0.001

	Sham Mean (± S.E.M.)		HWBV Mean (± S.E.M.)		Comparison Within Subjects			Comparison Between Subjects
	Intake	Discharge	Intake	Discharge	Sham	HWBV	Intake	Discharge
Visuospatial Working Memory	41.3 (8.0)	52.2 (8.3)	40.8 (2.8)	47.5 (3.7)	0.97	0.17	0.94	0.13
Spatial Short-Term Memory	43.5 (5.8)	44.5 (5.4)	46.9 (3.7)	43.9 (3.1)	0.97	0.58	0.91	0.94
Working Memory	48.3 (3.3)	49.5 (3.6)	46.1 (3.2)	51.4 (2.4)	0.97	0.17	0.91	0.84
Episodic Memory	37.5 (7.0)	43.3 (6.7)	37.1 (2.3)	42.3 (3.0)	0.97	0.29	0.94	0.94
Mental Rotations	58.8 (10.6)	50.3 (9.1)	32.9 (4.1)	54.0 (4.0)	0.97	8.0×10^{-6} ***	0.22	0.047 *

Visuospatial Processing	44.0 (4.4)	35.8 (3.8)	38.3 (3.7)	39.7 (2.9)	0.97	0.78	0.85	0.78
Deductive Reasoning	56.7 (5.2)	57.2 (5.0)	45.3 (3.5)	45.2 (3.2)	0.97	0.98	0.63	0.40
Spatial Planning	45.2 (9.2)	44.0 (9.7)	36.0 (3.3)	51.0 (4.5)	0.97	5.3×10^{-3} **	0.71	0.018 *
Verbal Reasoning	56.2 (10.6)	50.8 (7.8)	41.1 (4.9)	45.1 (5.3)	0.97	0.53	0.63	0.90
Verbal Short-Term Memory	36.3 (9.3)	36.5 (6.9)	39.3 (3.1)	41.7 (3.5)	0.97	0.58	0.91	0.84
Attention	33.0 (5.9)	39.0 (8.0)	38.9 (3.3)	42.8 (3.2)	0.97	0.50	0.85	0.95
Response Inhibition	45.2 (9.9)	33.5 (12.7)	29.9 (4.9)	46.0 (5.7)	0.88	5.3×10^{-3} **	0.63	0.018 *

Supplemental Table 5: Neuropsychiatric Testing Statistical Results; Comparison within subjects represents Benjamini-Hochberg false discovery rates (FDRs) from paired t-tests. Comparison between subjects at intake are FDRs from student's t-tests, and at discharge are FDRs from linear mixed models, using intake value and age as covariates. * FDR<0.05, ** FDR<0.01, *** FDR<0.001.