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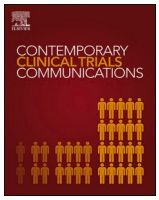

# Protocol for a pilot and feasibility randomized-controlled trial of four weeks of oral γ-aminobutyric acid (GABA) intake and its effect on pain and sleep in middle-to-older aged adults

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ABSTRACT

Approximately 1.71 billion people globally live with musculoskeletal pain conditions, including low back pain, knee pain, and neck pain Cieza et al. (2020). In the US, an estimated 20.4% of U.S. adult had chronic pain and 8.0% of U.S. adults had high-impact chronic pain, with higher prevalence associated with advancing age Dahlhamer et al. (2018). On the other hand, between 50 and 70 million US adults have a sleep disorder (American Sleep Association). Although the link between sleep and pain is widely established, the neurobiological mechanisms underlying this relationship have yet to be fully elucidated, specifically within an aged population. As currently available sleep and chronic pain therapies are only partially effective, novel treatment approaches are urgently needed. Given the potential mechanistic role of γ-aminobutyric acid (GABA) in both conditions, and the availability of GABA supplements over the counter, the present proposal will determine the feasibility and acceptability of oral GABA administration in middle-to-older aged adults with chronic pain and sleep disorders as well as characterize the potential neurobiological mechanisms involved in both conditions. Results from the present investigation using a parallel, double-blinded, placebo-controlled study will provide novel preliminary information needed for future translational pain and sleep research.

## 1. Introduction

Chronic pain is a serious public health problem affecting all age groups but, generally, peaking in mid-to-older age [2]. Similarly, sleep quality changes with age with nearly half of older adults complaining of difficulty sleeping. These sleep changes seem to begin around middle age [4,6]. Although the bidirectional link between sleep and pain is widely established, the common underlying neurobiological mechanisms linking sleep and pain have yet to be fully elucidated, especially in aging. Current sleep and chronic pain therapies are only partially effective, hence, novel treatments targeting shared potential mechanisms for both conditions are urgently needed.

A potential shared mechanism linking poor sleep and chronic pain in older adults is Gamma-Aminobutyric Acid or γ-aminobutyric acid (GABA) deficiency. GABA is the most important inhibitory neurotransmitter of the central nervous system (CNS). It has a broad range of effects on the body with GABA levels being implicated in the modulation of stress, mood, sleep, and pain [7–9]. Specifically, previous studies have

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shown negative associations of brain GABA concentrations with sleep disorders and chronic pain independent of each other (see Fig. 1 for model) [10–16]. We have previously showed that older individuals with chronic pain had significantly lower brain GABA levels compared with older controls. These lower levels of prefrontal GABA were significantly associated with self-reported and experimental pain measures [17]. A separate study in the same older cohort further showed that older individuals with the highest chronic pain reports had the worst self-reported sleep quality [18]. Although it has been suggested that GABA does not cross the blood–brain barrier (BBB) [19,20], or only crosses in small amounts [21,22], more recent work suggests that abundant amounts of GABA may cross the BBB [23–25]. These newly described GABA-transporter systems in the brain may be accessible as a route for oral absorption of GABA analogues [26]. Furthermore, oral GABA administration may also impact the brain via the gut-brain axis [27]. Indeed, changes in EEG brain responses have been reported after oral GABA administration compared to water/L-theanine [28] and dextrin placebo controls [29]. Overall, these findings support the idea that increasing GABA levels (i.e., brain and systemic levels) could improve both pain and sleep; however, no study to date has tested the effects of oral GABA administration on pain and sleep among older adults.

This paper presents the protocol for a pilot and feasibility randomized controlled clinical trial of oral GABA administration among adults with musculoskeletal pain and poor sleep. We hypothesized that 4-week oral GABA administration will be a feasible and acceptable intervention in middle-to-older aged adults with the potential to significantly improve clinical and experimental pain and sleep quality (Fig. 1) laying the groundwork for future larger studies.

## 2. Material and methods

### 2.1. Overview of study design

This is a pilot double-blinded, placebo-controlled, randomized parallel group study to examine the feasibility and acceptability of four weeks of oral γ-aminobutyric acid (GABA) intake and its effect on pain and sleep. Fig. 2, provides a flow diagram of the protocol. Our study design was guided by recommendations of the IMMPACT group for clinical pain trials [30–33]. After initial telephone screening, eligible participants will undergo two 2.5-h baseline sessions (health/sensory, and neuroimaging) for the collection of clinical information, quantitative sensory testing (QST), and brain imaging data. During the intervention, participants will self-administer 500 mg of GABA or placebo (P) daily, by mouth, and will receive a phone call once per week for an assessment of adverse event and compliance. We decided to administer the lower dose of 500 mg daily since no significant adverse events have been reported in the literature, indicating that GABA oral supplements are safe at these doses. During the last week of the intervention period, two sessions will follow that will be identical to the baseline sessions. During the entire intervention period, participants will wear an OURA ring to objectively measure sleep quality.

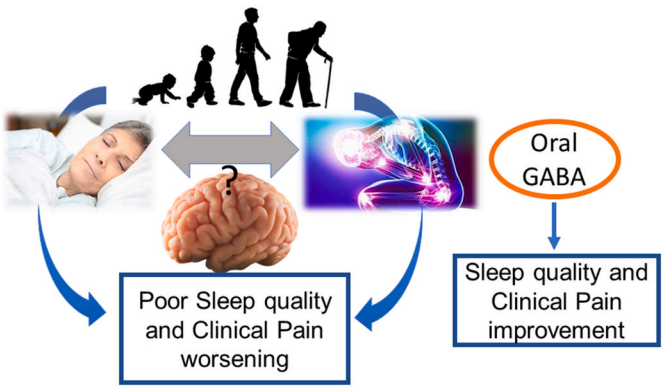


**Fig. 1.** Mechanistic working model.

### 2.2. Specific aims & hypotheses

Previous studies have shown negative associations between decreased brain GABA concentrations and sleep disorders and chronic pain independently [11,13,14,34–38]. Thus, our objective is to test the feasibility of examining the potential effect of oral GABA administration on sleep quality and pain in middle to older aged adults with chronic pain and poor sleep. It will also test the extent to which changes in various systemic and central nervous system mechanisms are involved in both conditions.

#### 2.2.1. Specific aim 1

To determine acceptability and feasibility of a four-week intervention with oral GABA. We will address this aim by assessing retention, baseline session attendance, and satisfaction with the study. We hypothesize that rates over 80% in retention, visit attendance, and levels of satisfaction will be indicative of a feasible and acceptable intervention in this population.

#### 2.2.2. Specific aim 2

To determine the effect of oral GABA administration on sleep quality as well as clinical and experimental pain. We hypothesize that compared to placebo, GABA treatment will result in clinically significant improvements (i.e., 50% changes) in: **H1a**) self-reported sleep quality; **H1b**) self-reported pain intensity; **H1c**) objective sleep measures; and **H1d**) experimental pain sensitivity.

#### 2.2.3. Specific aim 3

To characterize the neurobiological mechanisms contributing to the interindividual variability in both sleep restoration and pain relief. We hypothesize that compared to placebo, GABA administration will result in significant: **H2a)** increases in brain GABA levels; and **H2b)** increases in plasma GABA levels. Further, **H2c)** increases in GABA concentrations will be correlated to sleep quality and pain.

### 2.3. Study site

All assessments will be conducted at the University of Florida (UF) Health Sciences Center and the McKnight Brain Institute. This trial was approved by the University of Florida IRB (IRB202000105) and registered at ClinicalTrials.gov (NCT04683640). The study plans to utilize communication platforms to ensure the study team is sharing critical information and updates: 1) Weekly video conference meetings with the presence of investigators and staff, 2) Use of online platform Microsoft TEAMS to communicate study concerns, potential deviations, and problem solving. These methods are to benefit communication, quality of data, and minimize deviations. These resources provide timely responses between staff and investigators.

### 2.4. Participants

#### 2.4.1. Inclusion criteria

Older adults over 45 years of age who have a smartphone and have experienced pain of at least moderate intensity (>5/10 pain intensity ratings) on more days than not during the past three months, and who also reported poor sleep quality (>5 in the Pittsburgh Sleep Quality Index (PSQI)) will be considered for participation.

#### 2.4.2. Exclusion criteria

Participant exclusion criteria will align with study and safety requirements broadly related to GABA administration, pain and MRI and have been detailed in Table 1.

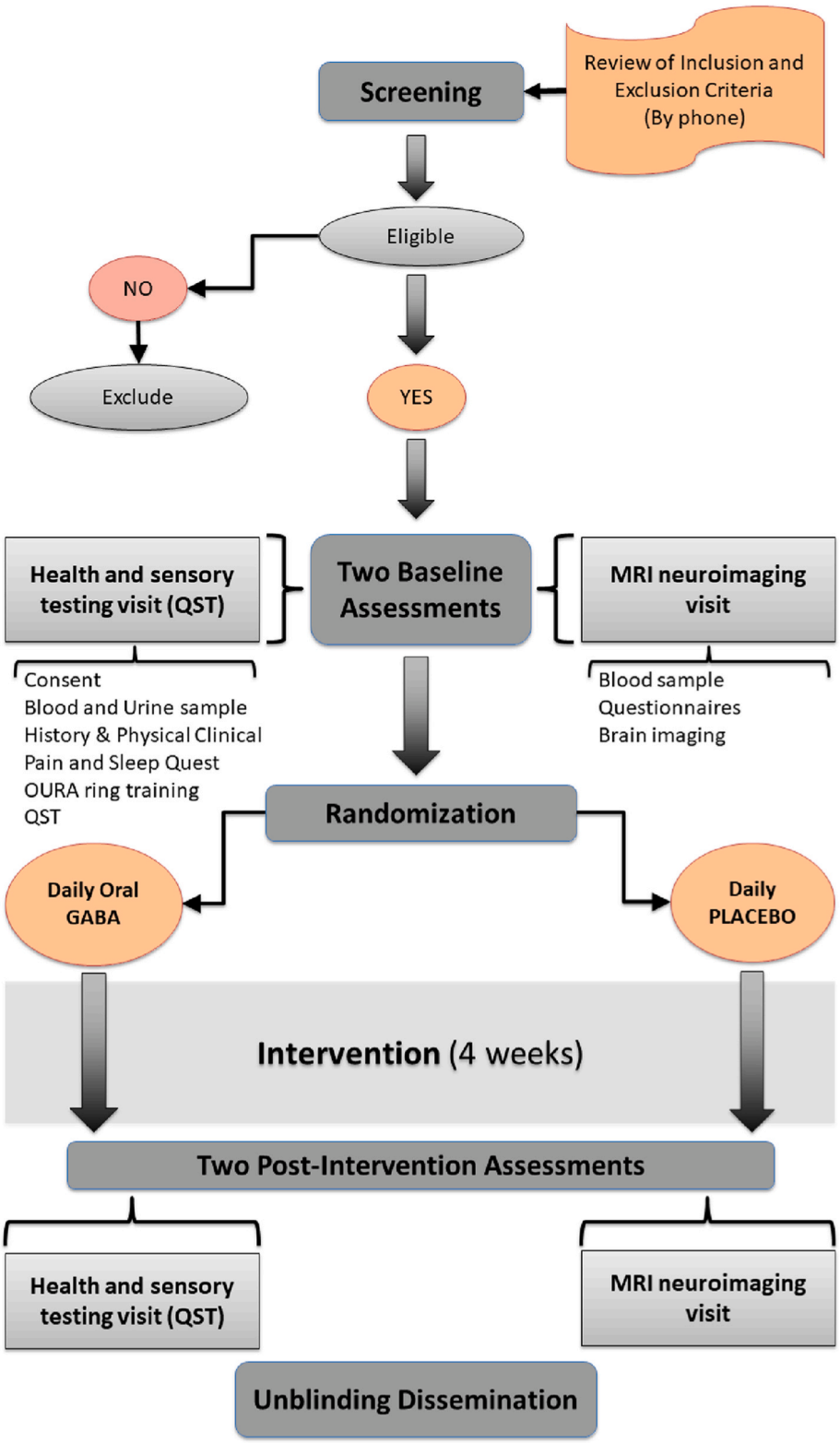


**Fig. 2.** Study procedures.

### 2.5. *Recruitment, screening and enrollment*

This study will adapt two types of recruitment plans: community-based and clinic-based strategies. Community-based strategy consists of a variety of efforts including recruitment flyers, local newspaper ads, radio ads, and ads in other print community-based media, as well as social media advertisement on Facebook. These adds will direct the user to call a lab-controlled phone number. Furthermore, the study will utilize clinical-based strategies by making use of various IRB-approved registries. Potential participants will undergo a computer-assisted telephone interview (CATI) to determine initial eligibility. Highly trained staff will conduct telephone interviews by using standardized approved scripts. These CATIs are divided into four parts: 1) explanation of study and obtaining verbal consent to proceed with the interview; 2)

**Table 1**
Exclusion criteria for the study participants.

| |
|---|
| 1) Inability to consent for study participation |
| 2) Pregnancy |
| 3) Significant cognitive impairment as evidenced by the Modified Mini-Mental State Examination [3MS] score ≤77 |
| 4) Serious psychiatric conditions e.g., schizophrenia, major depression, bipolar disorder |
| 5) Alzheimer, Parkinson, Epilepsy and other known intra-cerebral pathology and neurological conditions |
| 6) Hospitalizations for mental health reasons in the past year |
| 7) Serious systemic (uncontrolled diabetes self-reported HA1C > 7), (uncontrolled hypertension >155/90 mm Hg) rheumatic disorders (i.e., rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia), and HIV |
| 8) Arterial hypotension |
| 9) Digestive tract diseases |
| 10) Major medical surgery in the past two months, history of brain surgery or any serious brain condition like aneurysm, stroke, or seizures |
| 11) Excessive anxiety regarding protocol procedures |
| 12) Chronic/current use of narcotic medications, barbiturate, benzodiazepines and neuropathic pain medication including anticonvulsants and antidepressants |
| 13) Ingestion of sleep medications including those with zolpidem (Ambien and others) and eszopiclone (Lunesta and others) |
| 14) History of alcohol and drug abuse |
| 15) Current cancer diagnosis unless determined no evidence of disease or in remission for at least two years |
| 16) Allergies or sensitivity to GABA or its ingredients cellulose, gelatin (capsule), magnesium silicate, vegetable stearate and silica or to the placebo or its ingredients: calcium laurate, hypromellose capsule, magnesium (citrate), microcrystalline cellulose |
| 17) MRI contraindications including large pieces of metal in the body/face/neck and claustrophobia |

collection of information and demographic data; 3) review of criteria exclusion form; and 4) screening interview to determine eligibility. If the potential participant is deemed eligible, the first study visit will be scheduled, where verbal and written informed consent will be obtained and final eligibility will be determined.

### 2.6. Randomization and scheduling

Before their first study visit, a randomization will be assigned to the participant. Stratified block randomization (block size = 4) will be employed (block size = 4) such that for every 4 male participants (or every 4 female participants), 2 will be assigned to GABA treatment and the other 2 will be randomized to placebo. Such stratified randomization will ensure balanced GABA: placebo ratio (1:1) for both male and female groups. This stratified block randomization scheme and a randomization generation formula have been implemented in an Excel spread sheet, which will be accessed by the Investigational Drug Service (IDS) pharmacist who will independently enter the sex of the participant, that is the only stratification variable.

Upon study completion, the pharmacist will unblind the randomization record, providing access to investigators. The double-blinded nature of this study is ensured by having the pharmacist operate independently from the rest of the study team. In the event of adverse events in study participants, the pharmacy will be able to break the blind and inform treating physicians of group assignment.

### 2.7. Blinding & expectation management

As previously stated, the study is double-blinded, therefore, all participants and study staff will remain blinded. The pharmacist will be the only one unblinded and will not participate in collection of pre- or post-treatment outcome measures. Expectation management will be assisted by our staff delivering all study visits and outcome measures via reading scripts. To corroborate the blinding was adequate and properly maintained, at the last study visit, the participant will be asked what treatment they believe they were treated with: GABA or placebo.

### 2.8. Trial design

The treatment period will be four weeks of oral self-administration of either GABA or placebo (Fig. 2). Eligible participants will undergo two baseline sessions (health/sensory, and neuroimaging) for data collection involving a physical health assessment, Quantitative Sensory Testing (QST), and brain imaging. During the baseline health sensory session, individuals will be given an OURA ring (https://ouraring.com/) to collect objective sleep data during the intervention period. After the baseline neuroimaging session, participants will be randomly assigned either GABA or placebo to self-administer daily for four weeks. Blood samples will be collected at each baseline session. Participants will also be given a sleep diary and medication log to ensure that GABA/placebo is taken, and sleep habits are being recorded. Participants will be contacted weekly via phone call to complete a symptom checklist to assess for any adverse effects. In the last week of the intervention period (day 21–28), participants will attend two post-intervention sessions (health/sensory and neuroimaging) that are identical to the baseline sessions. After completion, participants will return materials and continue to be contacted 1 week, and 3 months via phone interview for a health checkup.

### 2.9. Pre-intervention

***Baseline Health & Sensory Assessment Session:*** After receiving the signed copy of the informed consent, participants will provide a fasting blood sample to evaluate standard clinical parameters (Comprehensive Metabolic Panel (CMP-14) Blood Test) and a Urine sample to measure urine specific gravity, which will be reviewed by a physician to determine study eligibility. For women under the age of 62, pregnancy tests will also be conducted. This session will take place in the mornings to accommodate for fasting and to control for circadian fluctuations. This session includes a physical examination and health assessment, clinical pain and sleep questionnaires and the QST assessment. Also, at the end of the session the participant will receive the OURA ring. The OURA ring is a smart device that participants can use the whole day, and especially when sleeping. We decided to use it because compared to other known devices OURA provides real-time tracking of vitals for longer periods of time without needing to be charged. OURA can be used for up to 7 days after one full charge and can be charged in full in 20–30 min. Further, OURA is not bulky and does not interfere with sleep as other devices, thus, its ease of use in this older population provides high compliance of use. Besides the OURA measures including sleep quality, readiness, daily activity, sleep duration, and heart rate variability; other important self-reported measures are included in our study.

***Baseline Neuroimaging Assessment:*** The neuroimaging assessment will occur within 30 days of the health & sensory assessment and is expected to last approximately 1 h. Details of the neuroimaging protocol are provided in section 3.3 below. At the beginning of this visit, subjects will complete some questionnaires related to the current pain experienced, general health and sleep quality since the last visit, as well as listing of all the current medications taken, and food eaten within the past 2–4 h. We will also collect a small blood sample to quantify circulating GABA concentrations. At the end of the session, participants will receive the GABA or placebo capsules.

### 2.10. Intervention

During the four-week intervention, participants will self-administer GABA 500 mg (two 250 mg capsules) or a placebo daily at home, at 08:00 p.m. The utilized natural-source GABA is a formulation developed by Thorne®. The Thorne® brand was chosen as the supplement meets both accreditation and quality standards, with certifications from Nutrition and Food Services (NSF), Therapeutic Goods Administration (TGA), and Good Manufacturing Practices (cGMP) certifications. The capsules are compounded free from major allergens like gluten, eggs,

tree nuts, and peanuts. Soy, dairy, yeast, shellfish, or fish are amongst the other ingredients not included. The inactive placebo will be compounded by the University of Florida Investigational Drug Services (UF, IDS) Pharmacy to ensure the same capsule size and color is used for both the GABA and the placebo. Compliance will be monitored by measuring the number of capsules left in the bottle after the treatment period, and via a log participant complete each day during the intervention. If at any time during the treatment it is determined that the participant should not continue due to adverse events, the study will be discontinued. Over the 4-week intervention period, participants will be contacted once a week to assess side effects. Any symptom reported as moderate or severe will be brought to the attention of the study principal investigators and will be discussed with the study medical doctors. These weekly calls will also ensure regimen compliance regarding study procedures (i.e., sleep diary completion, issues with OURA ring).

### 2.11. Post intervention

In the last week of the intervention phase, participants will be scheduled to return for their two post-intervention visits, which will be like the baseline visits. Importantly, at the follow-up Health and Sensory Assessment, we will assess changes in health status and their global impression of change since starting the intervention. At study closure, participants will also be asked to guess what study medication they were taking to assess the effectiveness of blinding, followed by a full debriefing regarding the study aims. All study participants will be financially compensated for their participation. Finally, one week and three months after the last treatment phase, participants will receive a follow-up phone call to determine if any side effects occurred.

## 3. Assessment and measures

### 3.1. Primary and secondary feasibility outcome

#### 3.1.1. Clinical pain

Our primary self-report clinical outcome will be the visual descriptive scale (VDS). This is a pain thermometer scale where the participant can point to the word on the thermometer that best shows how strong or severe their pain is. It has an anchor from no pain to pain as bad as could be [39]. This has been previously used in older adults with chronic musculoskeletal pain [40] and will assess changes in pain intensity before and after oral GABA administration.

We will also assess multiple secondary outcomes to characterize oral GABA effects in self-reported pain and physical function: 1) the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [41], commonly used in musculoskeletal pain in the lower extremities. assesses knee OA symptoms in the preceding 48 h, including pain, stiffness, and physical function; 2) the Oswestry Low Back Pain Disability questionnaire [42] as a measure of chronic low back pain; 3) the NIH Low Back Pain Minimal Dataset [43] as the recommended measure for chronic low back pain; 4) Pain-DETECT [44] will assess the degree of neuropathic pain experienced by our participants; and 5) the Short-form McGill Pain Questionnaire (SF-MPQ-2) [45,46] will provide a multidimensional measure of pain. These measures will provide a comprehensive assessment of musculoskeletal pain and are reliable, well-validated measures of pain in aging.

#### 3.1.2. Sleep

Sleep quality will be assessed with the Pittsburgh Sleep Quality Index (PSQI) [47] and PSQI total score will be our primary sleep outcome measure. This is a well validated instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep by measuring seven domains: 1) subjective sleep quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbances, 6) use of sleep medication, and 7) daytime dysfunction over the last month. Scoring of the answers is based on a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert Scale.

Secondary sleep measures include Berlin Questionnaire [48], Epworth Sleepiness Scale [49], PROMIS-Sleep Related Impairment Short Form 8a [50], and FOSQ-10: A Short Version of the Functional Outcomes of Sleep Questionnaire [51]. These measures will provide a comprehensive measure of self-reported sleep quality, as well as to measure waking alertness, and the impact of daytime sleepiness on activities of daily living.

### 3.2. Quantitative sensory testing (QST)

Participants will undergo QST to determine responses to mechanical and thermal stimuli and conditioned pain modulation (CPM). QST will be performed on standardized sites using anatomical landmarks. All tests will be demonstrated and explained before being performed. All participants will be tested on the hands and feet with additional standardized testing sites chosen to include painful areas. Patients' medications and current clinical pain will also be confirmed. All QST procedures will be implemented using an-MRI compatible TCS system (Manufactured by QST. Lab, https://www.qst-lab.eu/, France), and Algomed Algometer (Manufactured by Medoc, https://www.medoc-web.com/algomed).

***Mechanical testing procedures***: Pressure pain threshold (PPT) will be assessed at the ipsilateral quadriceps and trapezius muscles. For all PPT measurements, after an initial practice trial, three trials will be conducted, and their average will be computed for data analysis. Using a digital, handheld, clinical grade pressure algometer, the examiner will apply a constant rate (30 kPa/s) of pressure and the participant will press a button when the sensation first becomes painful, at which time the device records the pressure.

***Punctate Mechanical Pain:*** will be assessed at the left thenar eminence and the left foot 2nd metatarsal head using a nylon monofilament (Touchtest Sensory Evaluator 6.65) calibrated to bend at 300g of pressure. As in our previous studies [18,52,53], participants will provide a pain rating following a single contact, after which they will provide another pain rating following a series of ten contacts at a rate of one contact per second. The difference between the pain rating for the single versus multiple contacts reflects temporal summation of mechanical pain.

**Conditioned Pain Modulation (CPM):** will be used to assess pain-inhibitory function. The conditioning stimulus will be the cold pressor task applied to the right hand, which will be tailored for each participant to achieve a stimulus that produces moderate pain (i.e., a rating of 40 on the 0–100 scale) and can be tolerated for a 60-s period. The test stimulus will be heat pain applied to the opposite ventral forearm, at a stimulus intensity which produces moderate but tolerable pain. First, baseline heat pain responses will be assessed, after which the participant will immerse their hand in the cold-water bath for 60 s. Immediately afterwards the heat pain will again be applied to the opposite forearm and pain ratings will be obtained.

### 3.3. Brain imaging

Magnetic Resonance Imaging (MRI) data will be collected at the McKnight Brain Institute on the Advanced Magnetic Resonance Imaging and Spectroscopy (MRS) facility's Philips 3-T Ingenia Elition X scanner using a 32-channel radiofrequency coil. Participants are verbally asked their current pain level (range 0–100) while on the MRI table and before starting the scanning procedures. A T1 weighted 3D gradient echo structural scan with compressed SENSE (repetition time = 8.1 ms, echo time = 3.7 ms, and 1- mm isotropic voxels) was acquired for MRS voxel placement and segmentation. GABA-edited MRS data will be acquired using the HERMES (Hadamard-encoded MR spectroscopy) sequence. Briefly, the HERMES sequence includes several sub-experiments one which contains a dual-lobe editing pulse for GABA (ONGABA = 1.9 ppm), one for OFFGABA = 7.5 ppm deriving the GABA-edited spectra (i.

e., GABA + -). Additional HERMES parameters include total acquisition time = 10:48 min, TR = 2000 ms, TE = 80 ms, 20-ms editing pulse duration, averages = 320, 2048 data points, 2 kHz spectral width, and variable power and optimized relaxation delays water suppression. Shimming was performed using an interactive shim tool (Gruetter 1993). The prefrontal voxel (size 2.5 cm × 2.5 cm x 2.5 cm) will be placed medial on the axial plane, aligned with the genu of the corpus callosum, inclusive of the pregenual ACC and medial prefrontal cortex (i.e., mainly Brodmann areas 10 [i.e., the anterior-most portion of the prefrontal cortex].

## 4. Data and safety monitoring plan

The following procedures will be implemented to ensure data and participant safety. Study progress and safety will be reviewed by the principal investigators in collaboration with a physician, and the study MD. We will stop the intervention if 30% or more of the participants in the GABA condition report seven or more (out of forty-four) of the side effects at moderate to severe levels over more than 3 days as assessed during the weekly check-in phone calls. Data collected before stopping the intervention will be used for analysis. All participants who complete the intervention phase of the study will be followed up by phone calls for 7 days to ensure safety. Progress reports, including participant recruitment, retention/attrition, and adverse events will be provided to an Independent Safety Monitor for review on a bi-annual basis. The Independent Safety Monitor for this study will consist of an established senior investigator not associated with our study. A study end report will be compiled and will include a list and summary of adverse events. Also, this report will address: (1) whether adverse event rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The annual report will be signed by the Independent Safety Monitor and will be forwarded to the IRB, NIH, and FDA. The Data Safety Monitoring Plan will also require that all significant serious adverse events that may be possibly related to the study participants be reported to the IRB, FDA, and NIH within 48 h of the principal investigator's learning of the event. Besides, any unanticipated serious adverse event which increases the risk to participants or potential participants will be reported to the IRB and the NIH within 48 h of the principal investigators being informed about the event. This study will be stopped before its completion if: (1) the intervention is associated with adverse effects that significantly impact the risk-benefit ratio, (2) study recruitment or retention becomes futile, (3) any new information about the supplement and the adverse events becomes available during the trial that necessitates stopping the trial; or (4) if the independent safety monitor indicates stopping the trial is necessary due to adverse event frequency or severity.

## 5. Data management and analysis

### 5.1. Online data management system

Our study will employ a REDCap online data management system. This secure data portal includes range limits to enhance accuracy of data entry by the study staff. The system will generate reports for monitoring of enrollment, retention, and other important study metrics. The REDCap system is maintained by the UF Clinical and Translational Science Institute (CTSI).

### 5.2. Sample size

We plan to recruit 30 participants, 15 participants in each of the two randomly assigned treatment groups. Since any effect size estimated from a pilot study is unstable, it does not provide a useful estimation for power calculations. Therefore, the recommended approach is to base sample size calculations for efficacy studies on estimates of a clinically meaningful difference by consideration of what effect size would be necessary to change clinical behaviors and/or guideline recommendations. Clinically meaningful differences of 50% changes are recommended for pain [31,33].

### 5.3. Statistical analysis plan

We will employ a repeated pre-post analysis of variance to estimate the treatment effect in comparison to the placebo. Point estimates, p-values, and 95% confidence intervals of the treatment effects will also be reported. Sex and age will be adjusted as covariates. Since we have multiple endpoints, multiple comparisons will be corrected by using the Benjamini-Hochberg Procedure.

## 6. Conclusion

Although the bidirectional link between sleep and pain is widely established, the common underlying neurobiological mechanisms have yet to be fully elucidated, especially in aging. As currently available sleep and chronic pain therapies are only partially effective, novel treatment approaches are urgently needed. Our general goal in this pilot study is to determine the feasibility and acceptability of oral GABA administration and potential effects on sleep quality and pain in middle to older aged adults with chronic pain and poor sleep as well as to characterize the potential neurobiological mechanisms involved in both conditions. The pilot will provide novel and the preliminary information needed for future translational pain and sleep research.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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