Management of Chronic Low Back Pain in Older Adults Using Auricular Point Acupressure

NCT03589703

Version Date: 02/04/2022

UTHealth
The University of Texas
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IRB - eForm A – Protocol

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1. Abstract

To advance the use of non-pharmacologic pain-relief strategies, our collaborative team proposes the use of auricular point acupressure (APA)—a non-invasive, nonpharmacological and self-managed strategy originating from auricular acupuncture in Chinese medicine[10,11]—as an innovative solution for chronic low back pain (cLBP) in older adults. APA is an acupuncture-like stimulation of the ear using small seeds taped to specific ear points, instead of needles. APA only requires the participants to press on the seeds (to stimulate the specific ear points) three times per day for three minutes each time (nine minutes total per day). This test protocol has consistently provided rapid pain relief (i.e., 1–2 minutes after ear stimulation),[7,8,12,13] which has encouraged patients to continue using APA to self-manage their pain.

Almost one-third (30%) of persons 65 years of age and older suffer from cLBP, which causes a significant negative impact on individuals and society in the U.S..[14] The goal of managing cLBP is decreased pain and disability.[15] To accomplish this, cLBP sufferers often use analgesics including opioids to decrease pain and facilitate activity, but the side effects caused by these medications are problematic.[16-20] Given the opioid epidemic in the U.S., pharmacologic strategies for managing chronic pain are challenged.[21-25] The Institute of Medicine[26] and Centers for Disease Control and Prevention[27] provide guidelines for non-pharmacologic and self-management strategies to treat chronic pain. However, patient, provider, and system factors, including patient buy-in and motivation, time intensiveness of office visits, insurance coverage and accessibility to care, often limit adherence to these evidence-based guidelines.[28-35] Importantly, older adults are less likely to receive adjunctive care (e.g., spinal manipulation or massage therapy) for cLBP.[36,37] Improving access to non-pharmacologic strategies is crucial to decrease the burden of cLBP in older adults.

Our team's pilot data shows that using APA in older adults with cLBP resulted in 40% less pain one day after starting APA.[9] We found that a four-week treatment achieves even greater pain relief (44% reduction) as well as improved function, both of which are maintained at the one-month follow-up.[9] Blood-level reduction in pro-inflammatory cytokines (e.g., IL-β) and calcitonin gene-related peptide (CGRP) and increased anti-inflammatory cytokines (e.g., IL-4) suggest APA impacts neural-immune signaling.[38,39] Further, we have developed and piloted a smartphone application (app) of ecological momentary assessment (EMA) to collect real-time cLBP outcomes associated with APA, with good usability reported by patients, which limits recall bias.[40] Pilot data combined with the feasibility of implementing APA widely in clinical practice provide the impetus for pursuing the next stage of research—evaluating the sustained efficacy of APA for cLBP.

We propose a randomized controlled trial to: (1) determine the efficacy of APA in relieving cLBP, and (2) examine the physiological impact of APA on cLBP in 200 adults 65 years or older (n=200 will be able to provide 90% power to detect 30% function improvement). To address possible placebo effects of treatment (i.e., point specificity) and nonspecific psychological factors (i.e., treatment beliefs,[41-44] expectations,[45,46] and patient-provider relationship[47,48]), we will use a three-group design: (1) *APA* (active ear points relative to cLBP), (2) *Comparison Group (CG)-1* (non-active points, not related to cLPB), (3) *CG-2* (enhanced educational control). Our EMA app will be used to monitor APA adherence and capture daily momentary cLBP outcomes and analgesic use.[40] Outcomes will be measured via EMA, weekly during intervention, 1-month after completion of APA (primary endpoint), and monthly follow-up up to 12-months to assess sustained effects. Our approach addresses the mission of the National Institute on Aging, the standardized research approach on cLBP suggested by the NIH Pain Consortium Research

Task Force[49] and the Surgeon General's challenge to limit prescription of opioids by providing a nonpharmacological strategy.[50]

2. Objectives (include all primary and secondary objectives)

- **Specific Aim 1.** Determine the efficacy of APA for relieving cLBP at 1-month after completion of APA (primary endpoint) and explore monthly follow-up to 12-months to assess sustained effects of APA. ***Hypothesis a:*** the APA group will experience significant improvement in cLBP primary outcomes (i.e., pain intensity, pain interference, and physical function) compared to the CGs. ***Hypothesis b:*** the APA group will experience significant improvement in cLBP secondary outcomes (i.e., lower analgesic use [the use of over-the-counter and prescription analgesics including opioids], quality of life, satisfaction, anxiety, depression, fear/avoidance, catastrophizing, improved relaxation, and sleep) compared to the CGs.
- **Specific Aim 2.** Determine the effects of APA on inflammatory signaling in cLBP. ***Hypothesis:*** APA will decrease circulating pro-inflammatory biomarkers (i.e., IL-1β, CGRP) and increase anti-inflammatory cytokines (i.e., IL-4) compared to the CGs.
- **Specific Aim 3.** Examine the relationship among potential mediators and moderators influence beneficial effects of APA on cLBP. ***Hypothesis:*** APA-induced cLBP symptom reduction will be mediated by changes in circulating inflammatory biomarkers and moderated by nonspecific placebo effects, relevant biological variables (e.g., age, gender, BMI), ethnicity, marital status, and comorbid conditions (e.g., smoking).

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Chronic low back pain (cLBP) is a major health problem **and the most common pain condition among those 65 years of age or older in the U.S.**[14,37] Despite the development of pharmacological and nonpharmacological interventions, cLBP outcomes have not improved and disability rates continue to rise.[51] Associated healthcare expenditure for cLBP is over $253 billion annually, owing to medical care and disability-related productivity loss and wages.[26] Compared to those in middle-age, older adults have a higher prevalence of cLBP, with longer symptom duration and greater associated disability and depression[37,52] and multiple medical conditions that require multiple medications. Poly-pharmacy may further aggravate symptoms and lead to additional problems such as adverse drug reactions and interactions.[53] In this proposed study, nonspecific cLBP will be used because a definitive diagnosis of the cause of cLBP cannot be made in up to 85% of patients and it is an accepted medical diagnosis.[5] The heterogeneous nature of cLBP will increase external validity, allowing findings to be generalizable to larger populations.

APA originates from Traditional Chinese Medicine (TCM) and is derived from auricular acupuncture. Auricular acupuncture was developed into a science in the 1980s by Paul Nogier, MD.[14-16] Dr. Nogier mapped a somatotopic representation of the human body onto the ear. In other words, specific points of the ear correspond to specific organs and areas of the body. In Nogier's system of diagnosis, the location of points on the ear corresponding to the symptomatic body is confirmed by electrodermal responses using an electrical point finder.[17,18] We have developed auricular diagnosis, a systematic and detailed APA protocol to locate ear points for treatment (for details see RESEARCH DESIGN).[17] Once identified, these points can be stimulated—classically with acupuncture needles and/or electrically[18,19] or, alternatively, with pressure via APA.[20] By stimulating these points, symptomatic parts of the body can be treated. [17,18] The underlying theory of auricular acupuncture posits that nerves in the outer ear correspond to specific areas of the brain, and these areas have a reflex connection with specific parts of the body.[18,19] This correlation of ear points and brain activity has been validated by functional MRI.[21,22] The therapeutic benefits of auricular acupuncture on pain have been recognized by the World Health Organization (WHO).[23] In 1990, the WHO established a standardized, internationally accepted nomenclature of ear points and their locations.[23] Auricular acupuncture has drawn interest and uptake from multiple agencies. For example, the Department of Defense (DoD) and Veteran Affairs (VA) have developed auricular battlefield acupuncture (ear

acupuncture)[83,84] to teach physicians, nurses, and other health providers that have pain management responsibilities for wounded warriors and further developed it into a curriculum to teach VA healthcare providers in 2013.[83] Dissemination of auricular acupuncture is limited by the invasive acupuncture procedure with needles and by the few and small sample sizes of randomized clinical trials. Therefore, we propose APA as a non-invasive and active treatment (self-management) for patients with cLBP as an alternative to auricular needle acupuncture.

APA is consistent with evidence-based chronic pain theory (e.g., self-management and empowerment of an active approach). It has been well documented that patients with chronic pain who take an active role in their treatment have superior outcomes compared to those who take a passive approach.[87,88] That is, patients adopting a "fix me" mentality to managing chronic pain—seeking out only passive interventions (e.g., medication, injections, acupuncture, massage, chiropractic care)—have a poor prognosis for recovery (i.e., experiencing sustained improvement in function despite persistence of some pain). With APA, after a therapist has applied the seeds, patients stimulate points by pressing on the taped seeds as directed to achieve acupuncture-like effects. For patients, the initial seed application is passive (i.e., the therapist places the seeds, with no effort required by the patient), but subsequently the patient must stimulate the seeds by applying pressure to them with their fingers to achieve sustained analgesia, thus encouraging an active approach to managing their pain. The immediate pain relief provided by APA also motivates patients to engage in this treatment.[8]

Table 1. APA Outcomes for Pain Intensity

	APA		Sham	
	Mean(SD)	Change	Mean(SD)	Change
cLBP (n=61)[8]	-3.53(2.66)↓	44%	-0.77(1.41)↓	8%
BC (n=31)[85]	-4.23(2.62)↓	52%	-1.54(2.96)↓	11%
AIA (n=20)[86]	-4.25(0.96)↓	53%	0.00(0.82)	0%

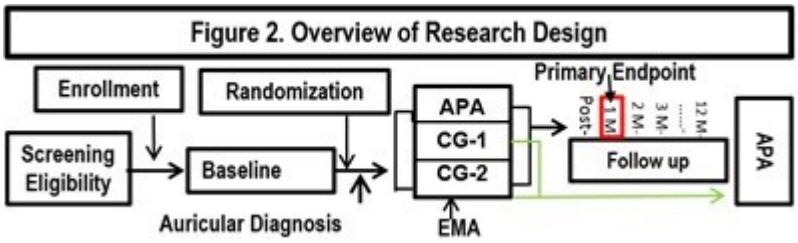
Evidence supporting the use of auricular acupressure and acupuncture for chronic pain shows promise but larger studies that address methodological issues are needed. Studies of auricular acupressure or acupuncture have demonstrated promising efficacy for pain management. We conducted pilot studies in APA: (1) individuals with chronic low back pain (cLBP),[7-9] (2) breast cancer (BC) patients with persistent post-mastectomy pain,[85] and (3) postmenopausal breast cancer survivors with aromatase inhibitor arthralgia (AIA).[86] All of our pilot studies demonstrated better than a clinically significant difference of pain reduction (defined as a 30% reduction)[89] after 4 weeks of APA (Table 1) and sustained effects for 1-month follow-up. Our pilot data also show blood-level reduction in pro-inflammatory cytokines (e.g., IL-β) and calcitonin gene-related peptide (CGRP), and increased anti-inflammatory cytokines (e.g., IL-4) suggest APA impacts neural-immune signaling.[38,39] A meta-analysis (17 studies including three conducted in the U.S.[90-92]) found evidence that auricular acupuncture reduces analgesic use in perioperative settings as well as other forms of acute and chronic pain.[6] In our meta-analysis of 13 studies of auricular acupressure and acupuncture for pain management, auricular acupressure and acupuncture provided significant pain reduction compared to sham or control groups (standardized mean difference [SMD] of -1.59, 806 participants across 13 trials).[4] Among four APA studies (275 participants) included in the meta-analysis, we observed a large effect size of APA, with a standardized mean difference of -1.85, indicating that the mean decrease in pain score for APA was on average 1.85 standard deviations greater than that in the sham control.[4] Evidence supporting APA remains limited: few studies were RCTs (only 4 APA were included in the meta-analysis), sample sizes tended to be small, short-term follow-up, blinding procedures were inadequate, and several studies lacked sham group comparisons. *Additionally, we cannot assume the beneficial effects of body or auricular acupuncture for pain relief will simply translate to APA because the stimulation between needle and acupressure may differ.* Evidence points to several potential biological mechanisms of action for APA. Neurophysiological connections between ear points and the human central nervous system have been supported by fMRI.[21,22] Similar to acupuncture, APA can change autonomic function, including heart rate and heart rate variability.[25,26] We have gathered preliminary data that support the existence of a neural immune pathway that interrelates the ear microsystem and somatotopic brain areas (i.e., decreased pro-inflammatory cytokines [IL-β, IL-2, IL-6] and increased anti-inflammatory cytokines [IL-4] in serum) in patients with chronic low back pain, suggesting that APA impacts neuro-immune signaling.[27,28]

supports the increases of peripheral pro-inflammatory cytokine levels corresponding with cLBP,[29-31] we hypothesize that the APA effects on altering inflammatory cytokines has the potential to treat cLBP.

Studies have demonstrated changes in heat, pressure, and mechanical pain thresholds immediately following acupuncture.[32,40-44] Brain imaging studies in acupuncture indicate that acupuncture can restore normal functional connectivity related to pain reduction.[32,34,45] In conjunction with our pilot data demonstrating that APA impacts neural-immune signaling in patients with chronic low back pain,[27,28] we hypothesize that APA may likewise induce pain relief through the stimulation of Aδ and/or C fibers to increase the pain threshold, endogenous opioid binding (releasing inflammatory cytokines), and alter brain networks of central processing in the hypothalamic-pituitary-adrenocortical axis to achieve analgesia.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).



This prospective randomized controlled study, will randomly assigned 200 participants into three groups: (1) *APA* (active points related to cLBP), (2) *Comparison Group (CG)-1* (non-active points, unrelated to cLBP), (3) *CG-2* (enhanced educational control, an educational booklet on cLBP will be given and the treatment used by participants for their cLBP will be recorded) (Fig. 1). Participants at CG-1 and CG-2 will have the opportunity to receive APA after completion of the study assessment. The EMA smartphone app will be used to collect real-time cLBP outcomes and adherence to APA practice. Treatment and nonspecific psychological placebo effects will be measured via questionnaires for all participants. Considering that the best evidence of the efficacy of acupuncture can last for 12 months after treatment,[3] suggesting the potential APA effects, this proposed trial will evaluate the APA sustained effects for cLBP at 12-month follow-up. To avoid participant drop out, monthly phone follow-up will be used to collect study outcomes. Blood will be collected during office visits at baseline, post-APA treatment, and follow-up office visits at 1-, 3-, 6-, 9- and 12-months post-completion of treatment for a total of 7 assessments. Appointments will start between 9 and 11 am to control for circadian variation in cytokine levels.[146,147] All proposed techniques have been established in our feasibility trial.[7,9]

Study Population: Participants will comprise: (1) over 360 patients 65 years of age or older who are diagnosed with cLBP (March, 2017) in the Healthy Aging Studies Unit registry, (2) over 3,000 older adults yearly (from UTHealth), and (3) 3,900 from direct mailing (13,000 households of which 30% have cLBP). Given the diverse demographics of Houson (45% Hispanic, 23% African-American)[148] and of outpatient visits at UTHealth clinics, we anticipate that we will recruit at least 35% minority participants. The male/female distribution corresponding to the most recent Houston, TX, census shows that females comprise 50.1% of the population, and males 49.9%.[148]

Study Site. The study will be conducted at the Cizik School of Nursing. The clinic has consultation rooms where face-to-face interaction with patients can occur. The clinic is staffed by nurses, nursing assistants, and reception staff.

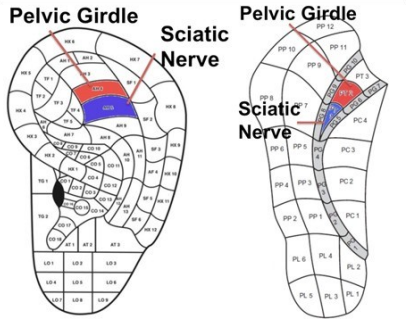
We plan to advertise through on-line and newspaper ads, study flyers distributed at outpatient clinics at UT Health, social media (e.g., Craigslist), and the clinical trials.gov website. We will use the registry of the Healthy Aging Studies Unit (currently over 1,200 patients registered).

While no scientific studies of auricular acupuncture or APA have reported long-term effects (1 year), we estimate 12-month effects of APA on lower back pain based on acupuncture literature.[3] Based on this rationale, we assume APA can sustain 90% effects at 12 months, the smallest effect size of physical function (0.65) would be 0.585 at 1 year follow-up. With a statistical power of 0.90, alpha level of 0.05 and 63

participants per group are needed to detect significant differences between intervention group and either Sham APA Control or Educational Control using a two-group repeated measures generalized linear model. We anticipate that approximately 30% of the enrolled participants will be lost to follow-up. Therefore, we will enroll 270 participants (90 per group). Due to high prevalence of chronic low back pain and our estimate of potential participants, we are confident to achieve this new sample size target of 270. This sample size will provide 80% power to detect effect sizes of 0.40 or greater for inflammatory biomarkers at 1 month follow-up. We will revise the budget accordingly to this change.

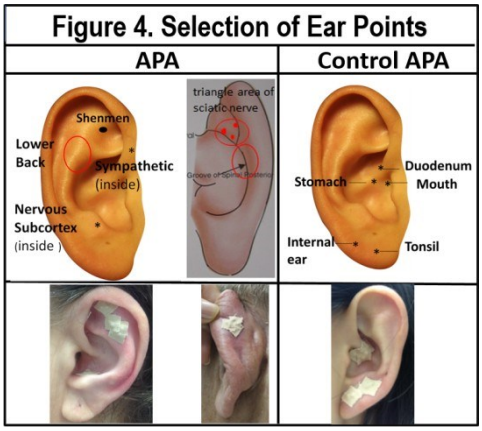
APA Treatment Protocol. Our APA protocol follows the International Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines.[150] Auricular diagnosis, a systematic procedure,[81] will be used to locate ear points. The search of active ear points will begin within an ear zone area (recognized internationally)[11] corresponding to body locations. Subsequently, specific points will be located guided by the Chinese Standard Ear-Points Chart.[151] Both sides of the ear will be used. The selection of specific points on the ear for treating cLBP centers on identifying the *active corresponding ear points* among all the points located in a particular ear zone related to the lower back (Fig. 3 and Fig. 4).[81,104]

Figure 3. Target Zones



Dose of Treatment and Frequency of Treatment Visits. Participants assigned to APA and CG-1 will be instructed to evenly press the tape and seeds covering each ear point without rubbing (to avoid skin damage and infection at the acupuncture point) for 3 minutes per time, three times daily (9 minutes total), even if they do not experience pain. A 2-second pause occurs between two pressings. The optimal pressure is considered to have been achieved when the participants feel localized tingling or mild discomfort. The tape and seeds will remain on ear points for 5 days. Participants will be instructed to remove both at the end of the 5th day. The interventionist will demonstrate the pressing technique to the participants, instructing them to apply steady pressure on the taped seeds until either mild discomfort or tingling is felt. Subsequently, the participants will do the pressing themselves. Patients will be instructed to contact the study center immediately and return for re-inspection, adjustment, and/or possible removal of the tapes if any adverse effects happen.

Figure 4. Selection of Ear Points



Randomization. After baseline data have been collected, all eligible participants will be randomized into three groups. The randomization process will be performed by a systems analyst and statistician through the use of statistical software equipped with a random-number generator to create a list of group assignments before the study recruitment begins. This procedure will allow real-time randomization to occur immediately after baseline assessments. Randomization will occur in blocks of three or six, with assignments based on the specific number of expected eligible participants and divided equally between the three groups. The program locates the first unassigned record in the randomization list and assigns the participant to the group designated in that record. Participant identifier and date are written on the record.

Study Measures.

We will use the minimal data set to measure cLBP outcomes (PROMIS 29 Profile), which is recommended by NIH-Pain-RTF.[49] Participants can complete the data set within 7–10 minutes.[49] Mini-Mental State Examination[153] will be used to screen for cognitive function. We will also include measures of HRQoL, satisfaction, treatment beliefs and expectations, sleep, relaxation effects, catastrophizing and fear/avoidance, and placebo effects (Table 4). A paperless data entry system, installed in iPads, will be used to allow data to be directly entered into the database. Additionally, participants will be interviewed to discuss their experiences of the APA. Open-ended questions will be used for the interview, such as (1) how do you feel about the APA? (2) do you have any difficulty to press the seeds at home? (3) Is there any methods to improve the APA for your help, (4) any comments for the APA? The interview will be tape-recorded. The interview data will be transcribed and saved as the word documents for the content analysis.

Table 4. Summary of Study Measures

Construct	Specific Measure	# Items	Reliability & Validity	Timing
SCREENING				
	Mini-Mental State Examination		Good[153]	ǂ
PRIMARY OUTCOMES: Pain intensity, Pain Interference, Physical Function				
	Minimal Data Set	4	Good[49]	ǂ, ǂ
SECONDARY OUTCOMES				
Analgesic Use	Quantification Score Version III		Objective[154]	ǂ, ǂ
HRQoL	Health-Related Quality of Life	36	High[155]	ǂ
Satisfaction	Treatment Satisfaction	12	Good[7,9]	4wk only
Psychological				
Anxiety, Depression	Minimal Data Set	8	Good[49]	ǂ
Fear/Avoidance	Fear Avoidance Beliefs	16	Good[156]	ǂ
Catastrophizing	Pain Catastrophizing Scale	13	Good[157]	ǂ
Behavioral				
Sleep	Minimal Data Set		Good[49]	
Relaxation	Relaxation Response	1	Pilot study	ǂ
MODERATING VARIABLES: Comorbidity, Demographics				
	Minimal Data Set		Good[49]	Baseline
NONSPECIFIC PSYCHOLOGICAL PLACEBO EFFECTS				
Expectation, Belief	Treatment Expectation	2	Good[7,9]	Baseline
Relationship	Patient-Provider Relationship	7	Good[158]	ǂ

▫ EMA; ǂ Baseline, post completion of treatment , monthly follow-up for 3 months

EMA. Each participant will be provided a smartphone and charger and instructed to use the EMA daily and charge the smartphone each evening. We will revise and customize our EMA app[40] to enhance user-friendliness, enlarged font size screen, and volume control to optimize use for older adults. The data collected through EMA will be used to calculate participants' (1) frequency and duration of APA practice, and (2) medication use and clinical outcomes (i.e., pain intensity, pain interference, and physical function), each measured by one question. The EMA app will include two surveys addressing: (1) random EMA of the real-time outcomes (pain intensity, pain interference, and physical function) and (2) time-contingent EMA for the adherence of APA practice and analgesic use, which will be prompted according to the participant's schedule. The random EMA survey will be programmed to deliver one random prompt per day during waking hours commensurate with each participant's schedule. The four items addressing momentary pain/function level can be completed within 1 min. Time-contingent EMA survey entries of APA practice and analgesic use will take under 2 min to complete. Adherence will be calculated by the proportion of EMA completed and proportion of days in which APA practice goals are met. EMA questions will be presented one at a time on the screen (See Appendix B, screen shots). Participants will respond to each question by using the touch screen to move the cursor forward and back and then exit the questionnaire. EMA data will automatically upload to the project website in real time via an economical cellphone carrier data plan, and it will be evaluated every 72 hours to determine usage. The smartphones selected will be designed to support the Android or iPhone operating system separately and feature a large high-resolution color LCD touch screen and non-volatile memory to avoid data loss in the event the battery discharges. Participants who do not enter EMA data for more than 2 days will be contacted to determine the reason, will be assisted in resolving any problems, and will then be encouraged to resume EMA recording..

Blood Sample Collection/Testing for Biomarkers. We will follow the protocol from our pilot studies for collecting and analyzing blood samples.[38,39] A 15 mL blood sample will be drawn at baseline, 4 weekly office visits after APA treatment, and follow-up at 1-, 3-, 6-, 9- and 12-months post-completion of APA (10 time points). Blood samples will be collected using standard phlebotomy procedures and processed

immediately for serum collection (coagulation and serum separation by centrifugation). Serum will be stored at -80 °C at the Cizik SON. All specimens will be multiplexed and duplicated in assays and analyzed using Bio-Plex Manager software. The serum levels of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IFN-γ, TNF-α, CGRP, and TGF-β will be measured using a multiplex bead-based immunofluorescence assay performed by a blinded technician (Luminex-200 system, Version IS, Luminex, Austin, TX). A five-parameter regression formula will be used to calculate the sample concentrations from the standard curves. The quantification of biomarkers will be performed in duplicate to verify the results. These assays typically exhibit high precision and reproducibility (i.e., 84.5% sensitivity, 98% specificity; 92% of the patients in the active disease group correctly classified from a cross-validation serum set).[159]

Timeline. The objectives and timeline of the proposed study are summarized in Table 5

Table 5. Timeline of the Proposed Study

	Year 1			Year 2			Year 3			Year 4			Year 5		
Months	1–4	5–8	9–12	13–16	17–20	21–24	25–28	29–32	33–36	37–40	41–44	45–48	49-52	53-56	57-60
Preparation, app reconfigure															
Recruitment, intervention, data collection, data entry															
Follow-up, data collection, entry, verification															
Data cleaning, data analyses, prepare abstract, manuscripts, final report															

Potential problems and strategies.

1. **Management of a Large-scale Study.** Dr. Yeh has the support of a cohesive team of experienced co-Is who are recognized in their areas of knowledge and have expertise complementary to this project.
2. **Adherence.** EMA data will be checked every 72 hours to determine usage. Participants who fail to respond to EMA prompts for more than 2 days will be contacted to determine the reason for not doing so.
3. **Fidelity.** Interventionists will demonstrate their proficiency with written and oral examinations and will be observed and mentored during training. The interventionists will take photos of every participant's ear after the seeds have been placed and the photos will be sent to the PI for comparison to her treatment prescription to maintain at least 95% accuracy for the first 20 participants, and will then be randomly selected to check for accuracy monthly during the study.
4. **Recruitment/Dropout.** Recruitment will be monitored closely. Changes in recruitment procedure will be made if lower-than-expected recruitment occurs. We will provide participants with free parking or transportation to facilitate coming to sessions, and reimburse them for their time. We will also call/reschedule when a treatment session is missed. Participants in the CGs will have opportunities to receive APA after they complete the study. For participants who decline further treatment or are unable to come in for follow-up assessments, we will contact them to complete questionnaire data by phone.
5. **Participant Burden.** We are aware that reducing participant burden is important. Although we did not have complaints of excessive burden in the pilot study and observed a 90% retention rate after receiving the first APA treatment, we have further minimized burden with the smartphone to collect the daily data.
6. **Measurement Errors.** Well-established measurements will be used. Data collectors will be trained to ensure standardized procedures; interventionists will be trained to ensure intervention fidelity.
7. **Loss of Blinding by Research Staff Involved in Data Collection.** Our pilot findings suggested good blinding. We have developed a diagram of study personnel, duties, and blinding status to demonstrate how we plan to maintain blinding.

5. Inclusion/Exclusion Criteria

Inclusion criteria	**Exclusion criteria**
• age 65 years or older • able to read and write English • cLBP that has persisted at least 3 months and pain on at least half of the days for the previous 6 months[49] • average intensity of pain ≥ 4 on a 11-point numerical pain scale in the previous week • have intact cognition (Mini-Mental State Examination, MMSE > 24) • willing to commit to 4-weekly study visits and up to 12-months follow-up. • able to apply pressure to the seeds with tapes on their ears	• malignant or autoimmune diseases (e.g., rheumatoid arthritis) • known acute compression fractures caused by osteoporosis, spinal stenosis, spondylolysis, or spondylolisthesis because these conditions may confound treatment effects or the interpretation of results • sciatica with leg pain greater than back pain • allergy to the tape • use of some types of hearing aids (size may obstruct the placement of seeds) • pain in other parts of the body that is more severe than the cLBP and which occurs daily or almost every day with at least moderate intensity or acute pain; neurological disorders that could interfere with pain reporting or confound performance on the other outcomes, cerebral tumor, Alzheimer's disease (or other cognitive illnesses), prior stroke, or multiple sclerosis

6. Drugs/ Substances/ Devices
N/A

7. Study Statistics

a. Primary outcome variable.

Adherence to APA practice, medication use, and real-time cLBP measurement of HRQoL, satisfaction, treatment beliefs and expectations, sleep, relaxation effects, catastrophizing and fear/avoidance.

b. Secondary outcome variables.

The serum levels of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IFN-γ, TNF-α, CGRP, and TGF-β

c. Statistical plan including sample size justification and interim data analysis.

The primary outcomes are measured at 1-month post-completion of treatment. In our pilot study (i.e., pain intensity, pain interference, and physical function),[9] Cohen's d (the effect sizes in terms of the standardized difference) ranged from 0.65 (physical function) to 1.28 (pain intensity) between the APA and the sham APA one month after intervention. Our pilot sham group (CG 1, non-reactive points) should have similar or better outcomes than CG 2 (enhanced usual care). The power calculation is based on the smallest observed effect size of 0.65 for a more conservative estimate for the sample size required in this proposed study to detect a difference between the active intervention and either of the control conditions. With 150 participants (50 participants in each of the three groups), we will be able to achieve 90% power to detect an effect size of .65 (between the APA and either of the CG arms) at a two-tailed significance level of 0.05. We anticipate that approximately 10% will be lost to follow-up at 1-month (primary endpoint) based on our pilot study[9] (10% dropout at 1-month follow-up after 4-week APA), and Dr. Szanton's R01 (11% after 5 months follow-up).[125] We plan to recruit 200 participants to allow for an adequate sample size in our exploratory analysis of the 12-month follow-up, assuming 25% of the enrolled sample will be lost to follow-up at 12-months. Achieving this sample size during a 42-months accrual period will require enrolling 58 participants per year, which should be feasible through our proposed recruitment strategies. With this sample size, we will be able to detect significant changes in some of the biomarkers (CGRP) but not all based on our pilot studies. We are collecting these to get a better estimate of the effect using a larger sample size.

Analysis plan for aim 1 will be to determine the efficacy of APA for cLBP at one month post treatment. For continuous outcomes, we will use a general linear mixed model (GLM) to construct a multilevel model for comparing the differences in the change in the outcomes from baseline to one month among the three groups. The group-by-time interaction is the main parameter of interest. This model will adjust for fixed

effects from important demographic and clinical covariates, if needed. Random effects from subject heterogeneity and temporal autocorrelation with the first-order autoregressive (AR(1)) covariance structure will be used to model the repeated measurements. The comparison of all outcome measures between, before, and after APA will assess possible treatment placebos (i.e., point specificity) and blindness of intervention. In addition to reporting mean score changes of outcomes reaching clinical significance, a cut point of 30% improvement for primary outcomes will be used for responder analysis.[49,165] For responder analysis of primary outcomes, we will adopt a generalized logistic mixed model[166] with the same fixed and random effects and AR(1) covariance structure. In both models, violation of assumptions will be detected by corresponding model diagnostics.[167,168] Using the approach outlined above, analyses will be conducted using the monthly data through 12 months to explore the maintenance of the effect over time. Quadratic terms will be included in the model to allow for non-linear change across time.
Analysis for aim two, evaluating the effect of APA on biomarkers, the analytical strategies for Specific Aim 1 will be used. Outcomes at one-month post treatment will be examined using each biomarker individually and two latent variables with pre-defined biomarkers within the groups of pro- and anti-inflammatory biomarkers. We hypothesize that the analgesic effects of APA are the aggregating and counter-interacting effects of different biomarkers within each latent variable. Before analysis, we will check the normality assumption in original data and log-transformed data. If normality cannot be met in both types of data, we will use two alternative approaches: we will apply a non-parametric test (e.g., Kruskal-Wallis test) to do multiple comparisons in each time difference among three groups; We will categorize the change of biomarker measurement into increase (recoded as 1) and decrease (recoded as 0) from baseline, and apply a GLM, which can handle repeated measurements and subject heterogeneity. To examine the sustained effect of the intervention over time in biomarkers (baseline, 1, 3, 6, 9, 12 months), we will use the approach described in Aim 1 using linear mixed models with quadratic terms to model the change in biomarkers across time. Each biomarker will be tested individually and the two latent variable within pro- and anti-inflammatory biomarkers as well.

Aim three analyses will examine the moderating effects of demographics, comorbid conditions, treatment, and placebo effects, as well as the mediating effects of biomarkers in both primary and secondary outcomes. To examine whether or not demographics, comorbid conditions, and placebo effects moderate the relationship between APA treatment on primary and secondary outcomes, the previously described regression models in Specific Aim 1, which include the main effect terms for the intervention or group, will be expanded to include the main effect terms for moderators and the three-way interaction terms between group, time, and moderators. Models will be simultaneously estimated under a framework of a mixed model structure by adding a covariance structure to consider possible correlations among biomarkers. Appropriate model statistics (e.g., estimated regression coefficients [with 95% confidence intervals] for the interaction terms, change statistics based on likelihood ratio test, and F-statistics) will be used to evaluate moderation effects. Latent variable models will be used to examine the mediation effect of inflammatory biomarkers. Group assignment will be the independent variable and change in outcome from baseline to 1-month post treatment will be the dependent variable. Change in inflammatory biomarkers from baseline to immediately post-intervention will be included in the model as a mediator. The parameter of interest will be the indirect effect of treatment group through inflammatory biomarkers on change in outcomes.

d. Early stopping rules.

We do not expect any adverse events related to the testing procedures as they have no remarkable health risks. However, we will report all adverse events and evaluate on a case-by-case basis whether the occurrence of a particular adverse event has implications for discontinuing the study to ensure participant safety and well-being. Patients are allowed to drop out from the study if they do not feel comfortable with the procedures or they have an allergic reaction to the tape used for APA.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency

Listed below are all major procedures and associated risk.

Auricular point acupressure

Patients' ear may feel discomfort when the seeds first apply but will diminish after a couple of days. While not common or present in literature, it is possible for the participants to develop a reaction to the seed or a first-time allergic reaction to the tape. In these cases, the participant will be withdrawn from the study immediately. Additionally, migration of the seed from the outer ear into the ear canal is extremely unlikely (no documentation in previous studies), but not impossible. The tape being used is a waterproof tape and will withstand all usual activities. The tape will be removed by the participant five days after application, and replaced at the following visit by the interventionist. This ensures that the tape will not be worn out and will not lose the adhesive property as it is regularly replaced.

Blood draw

Patient may feel minor discomfort at the injection site. Infrequent risk includes soreness to mild pain, bruise and/or bleeding at injection site; anxiety related to anticipation of needle stick; lightheadedness. Rare (Occurs in less than 1% or less than 1 out of 100 people): infection at the insertion site, fainting.

Questionnaires:

Minimal risks associated with completing questionnaires and diaries are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning. Participants are permitted to omit answering questions they find distressing.

b. Steps taken to minimize the risks.

Participants will be recruited through on-line and newspaper ads, study flyers distributed at outpatient clinics at UTHealth, social media (e.g., Craigslist), and the clinical trials.gov website. Potential participants will be fully informed of the purpose and activities involved in the research study during the screening process. Information from potential study participants that decide not to participate or are not eligible to participate will be deleted unless that individual consents to having their name, contact information, and general health information (e.g., diagnosis) kept in a study database for future study participation. Interested participants will be scheduled for an in-person visit, where written informed consent will be immediately obtained, prior to initiating any of the procedures. Project staff conducting informed consent will be appropriately trained by the PI, and will have completed formal coursework in the protection of human participants. The informed consent process will take place in a private location, and no time limits will be placed on the process. Potential participants will be encouraged to ask questions at any time. The protocol and informed consent forms will be approved by the IRB. Participants will be informed that they are free to discontinue participation in the study at any time, and that declining participation will in no way influence any current or future care they may receive. One copy of the signed consent form will be given to the patient and one will be kept in the study files for documentation.

All personnel involved in study procedures will be fully trained in the protocol. Regarding any discomfort that may result from completing study questionnaires, participants will be informed that they are free to refrain from answering any questions that make them uncomfortable or that they perceive as being particularly personal or sensitive. No participant will be considered ineligible due to declining to answer certain items or specific questionnaires.

A number of procedures will be in place to prevent a breach of confidentiality from taking place. All potential participants will be fully informed of their rights pertaining to disclosure of personal health information (PHI) in accordance with HIPPA regulations. Confidentiality will be maintained by assigning participants a study number and numerically coding all data. One hard copy file linking the code number with identifying information will be kept in a separate locked file with direct access available to the PI and project staff only. All records and research data will be kept in locked filing cabinets or computers. Only

summaries of group data will be reported in any publications or presentations, with no identification of individuals. These precautions should serve to minimize legal risks to participants.

c. Plan for reporting unanticipated problems or study deviations.

Any protocol deviations and/or adverse events will be systematically documented and reported immediately to the IRB. Adverse Event Reports and/or Case Report Forms will identify study participants by their initials and a unique study participant identifier. The participant's name will not be attached to any data. Copies of these forms will be stored in a locked office, which is only accessible to the PI and authorized personnel.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

As detailed below, the investigators are quite careful regarding the protection of confidentiality, and multiple procedures are in place to reduce the likelihood of a breach of confidentiality. However, there is a small risk that information about participants could become known to people outside of this study, and this risk is identified in the informed consent form.

e. Financial risks to the participants.

There are no financial costs to study participants for any of the procedures.

9. Benefits

While there are no likely direct and immediate benefits to the individual participants, subject's pain may relief if the intervention works.

Study participants will be paid (if the study is funded) for their time with care given to offering reasonable pay that is not excessive or coercive for those who are less advantaged. The goal of our study is to develop markers and assessment variables that will help to characterize risk for negative clinical outcomes following surgery. Enhancing our ability to improve clinical outcomes is likely to be viewed as an important result of the research. With the precautions and procedures to minimize risk as described in the previous section, we anticipate minimal complications and discomfort and believe the risk to benefit ratio to be favorable.

10. Payment and Remuneration

All participants will receive free parking, $20 each time to appreciate their time, if the study is funded (the proposal has submitted to NIH R01 pending).

11. Costs

There are no costs to study participants.

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