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Acupuncture as an adjunctive therapy in opioid use disorder

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Thesis

ACUPUNCTURE AS AN ADJUNCTIVE THERAPY IN OPIOID USE DISORDER

by

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ABSTRACT

Opioids have been used throughout history for pain management, as well as for recreational purposes. The use of opioids in the United States has significantly increased in the past several years,. As patients began to develop tolerance to opioids, a demand for new easily accessible opioids emerged, resulting in its illicit use. Thus, the opioid epidemic has experienced different waves with the current fourth wave involving the co-use of opioids and stimulants, resulting in a surge in overdose-related deaths. The COVID-19 pandemic further exacerbated the crisis by disrupting access to medication-assisted treatment. Efforts to address the epidemic include guides for prescription opioid use, increased access to pharmacotherapy, and reducing stigma associated with opioid use disorder.

With chronic pain management often relying on opioid prescriptions, there has been an increase in adverse outcomes and overdose-related deaths. As alternative therapies gain attention, acupuncture has emerged as a potential non-pharmacological intervention. While acupuncture's efficacy in managing pain has been studied extensively, there is a lack of research investigating its role as an adjunctive therapy with the use of methadone in patients undergoing opioid withdrawal. This study aims to investigate the effectiveness of acupuncture as an adjunct therapy to methadone maintenance treatment (MMT) in patients with opioid use disorder (OUD). Investigating

its effectiveness in conjunction with methadone will provide insights into its potential role in reducing opioid use and improving treatment outcomes.

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LIST OF ABBREVIATIONS

APS	American Pain Society
CBT	Cognitive Behavioral Therapy
CDC	Center of Disease Control
DEA	Drug Enforcement Agency
FDA	sFederal Drug and Administration
MAT	Medication Assisted Treatment
MMT	Methadone Maintenance Therapy
NCCAOM	National Certification Commission for Acupuncture and Oriental Medicine
NSAID	Non-steroidal anti-inflammatory drugs
ODD	Opioid Use Disorder
PDMP	Prescription Drug Monitoring Program
SAMHSA	Substance Abuse and Mental Health Administration
TCM	Traditional Chinese Medicine

INTRODUCTION

Background

The opioid epidemic remains at the forefront of public health crisis. Currently, many Americans suffer from chronic pain, including neck pain, lower back pain, and migraines. For management of this chronic pain, the most common approach has been opioids, such as Hydrocodone, Morphine, and Oxycodone, for relief. Consequently, there was a significant increase in opioid prescriptions from 1999 to 2012¹, as physicians sought to provide therapeutic relief for patients with chronic pain conditions. However, the surge in opioid prescriptions has placed a heavy economic burden on the healthcare system and has contributed to a rise in opioid-related deaths in recent years². As a result, healthcare agencies have started exploring alternative therapies to reduce opioid use, including the use of physical therapy, chiropractic manipulation, Cognitive Behavioral Therapy (CBT), and acupuncture. Acupuncture, which has been in practice for greater than 2000 years, has played a prominent role in ancient Chinese history as a treatment protocol and remains a viable non-pharmacological adjunctive therapeutic option for opioid use disorder.

Acupuncture involves the use of needles that are inserted in specific anatomical locations, or “meridians,” to provide an analgesic effect. Although the precise mechanism of acupuncture remains unclear, theories suggest it impacts endogenous opioid receptors, leading to pain modulation. Thus, several new studies have proposed acupuncture as a non-pharmacological intervention to address the opioid epidemic. While these studies have shown promising results in terms of reduced opioid use, there

are a limited number of investigations demonstrating the benefits of acupuncture as an adjunctive therapy with methadone for patients undergoing opioid withdrawal.

Statement of the Problem

The opioid epidemic continues to pose a significant economic and health burden on our society. We are now entering the fourth wave of the opioid epidemic and despite many policies and interventions placed to curb the crisis, there has been no apparent decrease in opioid-related deaths. While COVID-19 exacerbated this crisis, now that the pandemic is receding and society is returning to a pre-pandemic state, it is crucial to address the escalating concerns of the opioid crisis. Exploring alternative options in curbing opioid use remains a necessity and acupuncture represents a potential tool in our arsenal.

Currently, there is a gap in research within the United States on the use of acupuncture as an adjunctive therapy in the management of opioid use disorder. While significant research has been conducted on the efficacy of acupuncture in the management of pain, there is a scarcity of randomized controlled trials that specifically target patients with opioid use disorder. Most research has been performed in China, where acupuncture is already a widespread practice due to its ancient roots in Traditional Chinese Medicine (TCM). In these studies, acupuncture combined with methadone maintenance therapy (MMT) has been found to be effective in reducing relapses, withdrawal symptoms, and cravings. However, to further explore acupuncture as a

conservative therapy option, it is imperative that randomized controlled trials be performed in the United States.

Hypothesis

The addition of true acupuncture as an adjunctive therapy in subjects undergoing methadone maintenance treatment will result in decreased methadone dosages, a decrease in drug craving, a decrease in relapses, and an overall improved quality of life compared to those subjects receiving sham acupuncture.

Objectives and specific aims

The main purpose of this study is to investigate the effectiveness of acupuncture as an adjunctive therapy to MMT in patients with opioid use disorder. The study proposed in this paper aims to compare the outcomes between the experimental group receiving acupuncture and MMT and the control group receiving sham acupuncture and MMT.

The primary outcome measure is the dose of methadone required on a weekly basis and the drug craving assessed through the visual analogue scale (VAS). The secondary outcomes include weekly urinary drug screening tests and a quality-of-life survey, assessed using the Short-Form Survey (SF-36). Specific aims include:

1. To assess the impact of acupuncture as an adjunct therapy to MMT on reducing the required dose of methadone in patients with opioid use disorder
2. To evaluate the effect of acupuncture on drug craving as measured by the VAS

3. To examine the influence of acupuncture on drug use as determined by urine drug screening tests
4. To investigate the potential improvement in quality of life in patients receiving acupuncture in combination with MMT using the SF-36 questionnaire
5. To determine the feasibility and acceptability of acupuncture as an adjunct therapy to MMT in patients with opioid use disorder

REVIEW OF THE LITERATURE

Overview

History of the Opioid Epidemic

Opium is a substance derived from the poppy plant that has been used throughout history for management of pain and for recreational use. Opium is derived from the *Papaver somniferum* plant, which was originally indigenous to the Mesopotamian region. The earliest evidence of opium use was 8000 years ago in ancient Sumerian tablets, which show the use of these plants in a medicinal setting. The poppy plant has also been recorded for medicinal use in ancient Egyptian society in 5000 BCE. Hippocrates, known as the “Father of Clinical Medicine”, has described the use of plants, including poppy, in the treatment of several diseases, including for the management of pain. With the advent of transcontinental trading routes, poppy was introduced to other parts of the world and the active material, opium, was extracted for use in religious and recreational ceremonies. For example, the Sufi Muslims often used *hasish* (derived from cannabis) and opium in psychedelic rituals that involved reaffirming their connection to “God”³. The use of opium in the medical setting was introduced during the American Civil War, when morphine was used to treat wounded soldiers in the battlefield. These soldiers often developed dependency to opioids in the years following the war, however, not enough was known to curtail opioid use at that time⁴. In 1898, Bayer Company introduced heroin for use in pain management, claiming heroin was a “wonder drug” that had less addictive potential than morphine. Without any regulation on the use of these opioids, these medications began to be prescribed for many ailments. As the potent

analgesic effects of heroin became evident and patients developed tolerance, its illicit use began to rise. In response, the Harrison Narcotic Control Act of 1914 was enacted, encouraging physicians and patients to avoid heroin and other opioids. Nevertheless, heroin had already established itself as a popular street drug, known for its euphoric effects and leading to illegal trafficking and production. In 1931, the federal government finally banned heroin production. By this time, heroin had established itself as a drug of choice for recreation and overuse^{5,6}.

The opioid epidemic, as we know it today, originated in the 1980s, when there was a shift in attitudes towards pain management. The initial increase in opioid use in the early 1900s led to overreliance and misuse of these medications. As a response, there was a prevailing notion to decrease opioid consumption, resulting in patients being undermedicated for their pain. Patients with unexplained pain were thought to be delusional, resulting in these patients receiving inadequate management for chronic pain. Attitudes began to shift as patient advocacy groups and pain specialists began to raise awareness of their patients receiving insufficient treatment. These groups aimed to dispel the “opiophobia”, or irrational and undocumented fear that patients will become addicted to opioids⁷. One of the major institutions involved in opioid advocacy was the American Pain Society (APS), which began to refer to pain as the “fifth vital sign,” emphasizing the need for opioid use in pain management^{8,9}. As a result, pharmaceutical companies began to investigate the “safety” and efficacy of opioids, citing misleading information from the research studies being performed to promote their use. In 1996, Purdue introduced

OxyContin and heavily marketed this medication, leading to marked rise in the use and abuse of these drugs¹⁰. This launched the first wave of the opioid epidemic.

As opioid dependency increased, there was increasing demand for these medications. Heroin became a drug of choice as individuals began to search for readily available and cost-effective replacements. There was also a contemporaneous shift in the supply of heroin. Prior to 2000, the majority of heroin supplied to the United States was from Southeast Asia, Southwest Asia, Mexico, and America. However, in the 2000s, Colombia and Mexico became the primary suppliers, leading to decreased prices and greater accessibility to the drug. By 2010, there was a surge in overdose deaths associated with heroin use, marking the second wave of the opioid epidemic¹¹.

The third wave of the opioid epidemic began in 2013 and has been attributed to the rise in the production of synthetic opioids, particularly fentanyl. As government regulations tightened and the availability of prescription opioids decreased, fentanyl became an alternative for those seeking the effects of opioids. From 2010 to 2017, deaths from fentanyl and other synthetic opioids increased nearly ten-fold, from approximately 3,000 to over 28,446 deaths^{12,13}. Fentanyl gained popularity due to its affordability and ability to mix, or “lace”, with heroin and prescription opioids, resulting in increased potency. In response to the escalating crisis, the US government declared the opioid epidemic a public health emergency in 2017. Following this declaration, healthcare and government agencies began to establish guidelines to regulate the prescription of opioids. For example, the Center of Disease Control (CDC) released twelve guidelines in 2016 that were targeted towards physicians to provide a framework for their opioid prescribing

practices⁸. In addition, Prescription Drug Monitoring Programs (PDMP) were also implemented across nearly every state to minimize opioid prescriptions from multiple prescribers. Efforts were made to enhance access to pharmacotherapy options for the treatment of opioid use disorder, such as methadone, buprenorphine, and naloxone¹⁴. Moreover, there has been a large shift in the language and attitudes regarding patients with opioid use disorder, aiming to reduce the stigma that is associated with the condition. For example, instead of using terms such as “addict” and “substance abuser,” terminology that has associated negative connotation, healthcare practitioners have been encouraged to implement “person first” language. The terms “addict” and “substance abuser” were replaced with phrases such as “patient with a history of opioid use disorder,” which address the patients as individuals rather than defining them solely by their disorder⁸.

While many strategies have been implemented to curtail this crisis, the opioid epidemic continues to be a pressing public health concern. At present, the United States is entering a fourth wave of the opioid epidemic, in which opioids are being combined with psychostimulants, such as methamphetamine and cocaine, leading to surges in overdoses and death rates^{15,16}. It is unclear why co-use of opioids and stimulants are on the rise. The COVID-19 pandemic has exacerbated this crisis, as there has been a marked increase in drug use and overuse due to social isolation restrictions. For patients undergoing medication replacement therapy with methadone and/or buprenorphine, the pandemic served as a hurdle to obtaining their regular treatment. These medications are tightly regulated by federal agencies, including the Substance Abuse and Mental Health

Administration (SAMHSA) and the Drug Enforcement Agency (DEA). With government and healthcare facilities overburdened by the rise in Coronavirus, patients on medication assisted programs were unable to receive their medications, contributing to increased relapses in patients seeking treatment. Although telehealth services were expanded and regulations on methadone prescriptions were relaxed, there was a general hesitancy amongst individuals seeking treatment or those visiting healthcare facilities due to the widespread virus^{17,18}. Furthermore, underserved and homeless populations faced even greater barriers to healthcare access with the increasing social distancing protocol and a decreased ability of the healthcare system to accommodate them in their emergency services as they dealt with the brunt of the virus¹⁹.

The opioid epidemic continues to remain a major public health crisis in this decade. Despite best efforts in curtailing this crisis, opioid overdoses and deaths continue to pose a significant healthcare burden. Since prescription opioids are primarily used to treat acute and chronic pain, there has been a general shift in seeking alternative options for management of pain. Efforts have been made in initiating the use of conservative management with NSAID administration, physical therapy, CBT, and/or acupuncture before resorting to opioid prescriptions. Consequently, there has been a surge in research focused on exploring alternative therapies in recent years.

Physiology of pain and opioid addiction

An opioid is defined as a substance that binds to the opioid receptor in the nervous system. There are three classes of opioids: (1) endogenous opioids; (2) naturally

occurring opioids (such as opium derived from the poppy plant); and (3) semi-synthetic or synthetic opioids. Within the nervous system, there are three types of opioid receptors: mu, delta, and kappa receptors. Each receptor acts on distinct pathways to promote analgesia. The mu receptor, the primary receptor to which morphine binds, plays a significant role in analgesia and the brain's reward pathway^{20,21}. Binding to the mu receptor can also result in adverse effects, including respiratory depression, nausea, urinary retention, biliary spasm, and constipation; these effects are notably seen in opioid overdose²². The other opioid receptors, delta and kappa, have additional effects with delta receptors having hallucinogenic properties and kappa receptors promoting dysphoria. When opioids bind to the opioid receptors, they activate G-protein coupled receptors, resulting in closure of calcium channels and decreasing the excitatory signal from one neurotransmitter to another. This results in a decrease in the transmission of pain. Although the pathways involved in opioid receptor activation are more complex, the fundamental mechanism of action is based on their ability to decrease pain sensation at a molecular level.

There are two recognized types of pain: nociceptive pain and neuropathic pain. Nociceptive pain refers to pain that is elicited by tissue damage, resulting in a “dull, aching” sensation. Nociceptive pain usually resolves when the damage is healed or removed. When nociceptive stimuli reach the site of injury, inflammatory mediators, such as prostaglandins, arachidonic acid, and bradykinin, are released. These intermediates stimulate voltage gated sodium channels in the peripheral nervous system, activating A-delta and C fibers, which transmit signals to the dorsal column of the spinal

cord. These fibers release substance P, stimulating ascending tracts in the central nervous system and allowing signals to reach the brain.²⁵ On the other hand, neuropathic pain arises from nerve damage and is described as a “sharp, burning, electrical” sensation. Neuropathic pain accounts for approximately 15-25% of chronic pain patients and is especially debilitating because it lacks a specific target; it causes generalized, non-specific bodily pain that cannot be alleviated by removing the site of injury^{23,24}.

The major ascending CNS tracts involved in pain signaling are the lateral spinothalamic tract and the spinothalamic tract. The lateral spinothalamic tract ascends contralaterally to the pain stimuli and synapses within specific nuclei in the thalamus. The thalamus is the brain’s sensory station, receiving sensory input from the body and distributing these signals to various areas of the brain, which then elicit an appropriate response. The spinothalamic tract ascends both ipsilaterally and contralaterally and terminates at the hypothalamus. The hypothalamus is the body’s processing center for automatic functions, such as thirst, appetite, and sleep patterns.

Once the pain signal reaches the brain, the thalamus and hypothalamus transmit these signals to different areas within the cortex, enabling one to recognize the pain signals and generate appropriate responses²⁶. The nervous system contains multiple neuropeptides that can produce analgesia, including endogenous opioids or endorphins, such as beta endorphins, enkephalins, and dynorphin. These substances act on endogenous opioid receptors to decrease the perception of pain, resulting in significant analgesic effects²⁷.

Pain modulation occurs through pathways within the brain that interfere with pain transmission, utilizing descending tracts and endogenous opioids as signaling molecules. For instance, pathways originating from the frontal lobe and hypothalamus release endorphins in the gray matter of the third ventricle and aqueduct of Sylvius, reducing pain sensation. Additionally, interneurons release endogenous opioids to curb the transmission of pain signals from the peripheral nervous system to the cortex²⁸. Once the cortex has assessed this signal, descending tracts will travel to the site of injury, producing an appropriate response. Figure 1 provides a visual understanding of the ascending and descending pathways associated with pain²⁹.

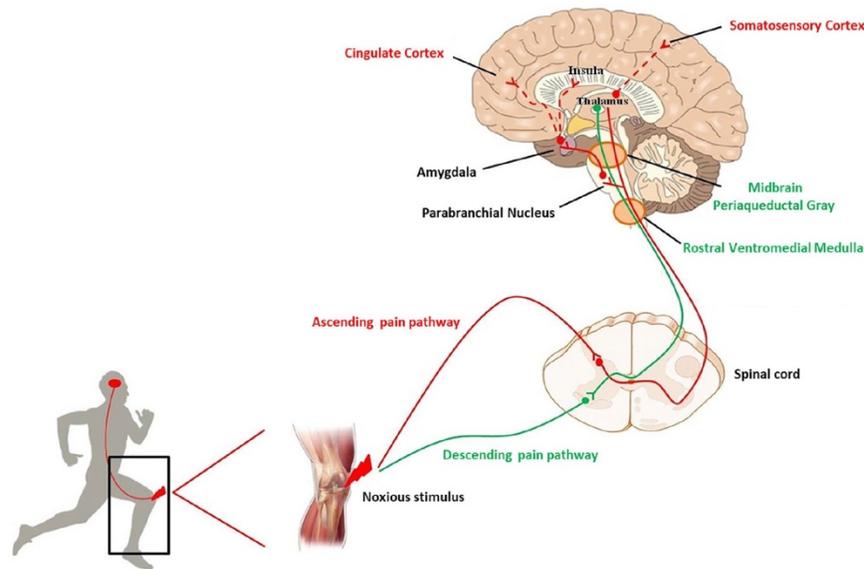


Figure 1: Schematic representation of ascending (red line) and descending (green line) pain pathways²⁹.

Pain is a very complex phenomenon and involves many hierarchical neural circuitry systems; limiting our understanding is due to the integration of multiple contributory modalities, including physiological, psychological, and emotional

components. The simplistic approach described herein provides a foundation for further exploration of alternative therapies, such as acupuncture, in mitigating pain and addressing the opioid epidemic crisis.

When opioids are first administered, they effectively reduce pain due to their analgesic properties. After repeated use, however, tolerance begins to develop. Tolerance occurs when opioid receptors become desensitized, requiring increased doses of opioids needed to achieve the same analgesic and euphoric effect that was experienced with initial use. One significant factor contributing to drug-seeking behavior is the activation of the brain's reward pathways through neurotransmitters, such as dopamine and serotonin. One of the most significant circuits involved is the ventral tegmental area (VTA)-nucleus accumbens pathway, which primarily utilizes dopamine. It is hypothesized that mu receptors are present on VTA GABA-ergic interneurons. Activation of these mu receptors leads to disinhibition of dopamine neurons, resulting in increased dopamine release and the pleasurable effects of opioid use³⁰. With repeated activation of the pathway, tolerance develops, necessitating higher opioid doses. In addition, dependence plays a pivotal role in the addiction process. Dependence refers to a state in which a person experiences withdrawal symptoms when opioid doses are reduced or discontinued abruptly. Withdrawal symptoms may include generalized pain, nausea, diarrhea, diaphoresis, mydriasis, tremors, restlessness, and anxiety. To avoid these adverse effects, patients continue using opioids. Both the mechanisms of tolerance and dependence contribute to patients' desire to escalate their opioid use, thereby increasing the risk of respiratory depression, overdose, and ultimately death.

While the pathway described is a very simplistic understanding and just one of many pathways found within our nervous system that reinforces drug seeking behavior, it is evident that the central nervous system plays a large role in both the positive and negative reinforcement that contributes to opioid use disorder. To combat and ease the severity of withdrawal symptoms, pharmacotherapy with opioid antagonists and opioid partial agonists is necessary. The Federal Drug and Administration (FDA) has approved Methadone, Buprenorphine, and Naltrexone as the gold standard medications for the treatment of opioid use disorder (OUD). The purpose of these medications is to help the patient through the initial phase of withdrawal, thereby making it easier for them to prevent relapse and remain sober. Methadone, first introduced in 1947, is an oral mu-opioid agonist, used as an alternative to opioids to alleviate the withdrawal symptoms from opioid use. Buprenorphine is a partial mu-opioid agonist that has a long half-life and is also used to manage withdrawal symptoms. Because both Methadone and Buprenorphine are long-acting and bind to opioid receptors, they both produce stable levels of the drug within the brain, while avoiding the rapid onset euphoria that is caused by recreational drugs, such as heroin or morphine. Naltrexone, on the other hand, is a competitive antagonist of the mu-opioid receptor and a partial agonist of the kappa-opioid receptor. While medication-assisted treatment (MAT) has been the standard of care for the treatment of OUD for the past several decades, there remains a high rate of relapse amongst patients. This necessitates a need to explore alternative treatment options and the utilization of a multidisciplinary approach to face the ongoing opioid epidemic.

Acupuncture

Acupuncture has been an integral aspect of Traditional Chinese Medicine (TCM) for 3000 years and is thought to play a role in modulating the pain signaling pathway and inducing analgesia. At its core, acupuncture involves the insertion of needles into specific points in the body, known as acupoints, which correspond to channels or meridians. In TCM, meridians, referred to as *Jing*, contain branches called *Luo* and encompass 361 acupoints throughout the body.^{31,32} The meridians and their collaterals form a network of channels that transport vital energy, or *qi*, and blood to regulate *ying* and *yang* flow, maintaining the body's harmony and balance. These meridians and collaterals are essentially linear pathways that run through the entire body from head to toe, connecting the interior organs to the exterior joints and skin. A patient who is experiencing illness is believed to have an imbalance or disruption in the flow of *qi* within the meridians. By stimulating the acupoints on the skin's surface, the flow of *qi* within the meridians can be influenced. This, in turn, induces changes in the internal organs, manifesting as the therapeutic effects of acupuncture.

While acupuncture has long been utilized in Western society as a therapeutic alternative therapeutic approach to pharmacotherapy for the treatment of pain and other disorders, the physiological and molecular mechanisms underlying its effects have remained elusive. It is thought that when organs undergo malfunctions, they transmit electrical signals through the meridians and to various acupoints³³ These acupoints correspond to specific pathologies. For example, low back pain is associated with the acupoints BL23, BL25, and BL60³⁴. It is worth noting that the meridians and their

acupoints have been integral components of TCM for thousands of years and the continued use and efficacy of acupuncture as a therapy attest to their effectiveness.

There are two primary methods of performing acupuncture: manual acupuncture and electroacupuncture (EA). Manual acupuncture involves the manipulation of needles by the practitioner, including inserting, withdrawing, and twisting of needles. This stimulates A-delta and C-fibers within the peripheral nervous system.

Electroacupuncture, on the other hand, applies electrical stimulation, using either high or low frequency impulses, to achieve the same effect. In a simplified explanation, the activation of these fibers trigger afferent signaling pathways, which travel to the dorsal horn of the spinal cord and ascend through specific pathways to reach areas of the thalamus and hypothalamus, where neuropeptides, including endogenous opioids, will be released. This is similar to the pain pathway previously described, suggesting that acupuncture may be based on a physiological phenomenon rather than a purely psychological concept³⁵.

Therefore, it is reasonable to hypothesize that acupuncture could serve as a viable approach to pain management, particularly for individuals with opioid use disorder. Opioids stimulate the release of endorphins, producing a sensation of analgesia and euphoria, which benefits those with chronic pain. Given that acupuncture works by increasing levels of endogenous opioids and endorphins in both the central and peripheral nervous system, it may have potential as an adjunctive therapy, enabling patients to reduce their reliance on opioids.

Existing research

While numerous trials have investigated the efficacy of acupuncture in treating various types of pain – chronic back pain, post-operative pain, cancer pain, migraines, osteoarthritis – there is a lack of widespread studies on the role of acupuncture in reducing opioid use among individuals with opioid use disorder. Most patients that are seeking treatment for opioid use disorder undergo medication therapies, including methadone and suboxone. However, these medications fail to provide the analgesic and euphoric effects like that of illicit opioids, resulting in high relapse rates. Although acupuncture is not intended to replace these medications, it can serve as an adjunctive therapy to help reduce relapses. Randomized controlled trials have been conducted to test these theories, however, results have been mixed; some studies suggest that acupuncture effectively reduces opioid cravings and aids in maintaining abstinence, while other studies report that acupuncture led to no significant difference.

Since acupuncture has long been used in the management of substance use disorder, there have been many studies conducted on the efficacy of acupuncture in decreasing substance use. While cocaine is not part of the opioid family, it is another illicit drug that has a high addictive potential. One of the largest studies was performed in 2002, utilizing 620 cocaine-dependent patients in a randomized controlled, single-blind clinical trial to investigate the role of acupuncture. The patients were assigned to receive auricular acupuncture, a needle-insertion control condition, or a relaxation control condition for eight weeks, along with drug counselling. The effectiveness of treatment

on drug use was determined through urine screenings. The overall odds ratio for a negative cocaine urine screen was 1.40 (95% confidence interval, 1.11-1.74), indicating that there was a 40% higher likelihood of a negative cocaine urine screen in the acupuncture group. However, the study overall showed that there was no statistical significance between acupuncture and the two control groups ($z = 0.005$, $P = 0.90$). The conclusion of this study implied that acupuncture was not more effective than other interventions for reducing cocaine use³⁶.

A study performed in 2009 explored the potential of auricular acupuncture as an adjunct to methadone detoxification to reduce the severity of opiate withdrawal and craving during treatment. The researchers selected 82 patients from an inpatient unit at a hospital in South London, where they received the treatment for 14 consecutive days with each session lasting 30-40 minutes. The intervention involved either auricular acupuncture or a placebo consisting of five metal clips, that were specifically designed for the study. Despite their efforts, the study findings indicated that auricular acupuncture did not have an impact on withdrawal responses during opiate detoxification. It is important to acknowledge the limitations of this experiment, particularly the relative short duration and timing of the intervention. The intervention was performed within the first fourteen days of withdrawal, when withdrawal symptoms are expected to be the highest. Additionally, there was selection bias, as the patients selected were from an inpatient setting, implying that these patients may have higher levels of opiate dependency and required greater care than what acupuncture could have provided for them³⁷.

Studies that have highlighted the effectiveness of acupuncture as an adjunctive therapy have predominantly been published in Chinese journals, which has limited their acceptance and availability in Western literature. A recent study conducted from 2019 to 2020 focused on patients from an addiction treatment center in the Department of Psychiatry and Chinese Medicine at Kaohsiung Chang Gung Memorial Hospital³⁸. The purpose of the study was to explore the effects of laser meridian massage on patients undergoing MMT and its potential to decrease heroin use and craving. The researchers selected a sample size of 28 patients, assuming a medium effect size of 0.25, an alpha level of 0.05, and a power of 0.80. Although the study observed a decrease in the positive rate of urinary morphine from 0.86 to 0.64, the overall difference between the experimental and control groups was not statistically different at 2 weeks ($p=0.082$) or 4 weeks ($p=0.165$) of treatment. However, the experimental group receiving laser meridian massage did exhibit a reduction in heroin craving. It is important to note that this study had limitations, such as the small sample size of 28 patients, which limits the generalizability of the findings. In addition, the study employed laser acupuncture instead of traditional acupuncture, which may not be as effective since traditional acupuncture relies on the sensation of *de qi* (numbness and soreness) elicited by needle placement. Nonetheless, the study provided promising preliminary findings.

One of the most promising studies in this field was conducted recently, from 2019 to 2020, at the Substance Dependence Department of Guangzhou Huiai Hospital. This study utilized a randomized-controlled trial (RCT) with 135 patients who were randomly assigned to either treatment group receiving acupuncture and MMT or a control group

receiving MMT alone. The effectiveness of the treatment was evaluated using daily dosage of methadone (measured at baseline, 2nd, 4th, and 6th week), the severity of opioid craving using a visual analog scale (VAS), sleep quality using Pittsburgh Sleep Quality Index (PSQ1), and quality of life using SF-36³⁹. Although the official results of the RCT have not been released yet, a preliminary cost-effectiveness analysis has provided us with some insights regarding this trial. The analysis indicated that the combination of acupuncture and MMT resulted in a significant reduction in the daily dosage of methadone, decreased drug cravings, and improved insomnia compared to MMT alone. The promising results may be reliant upon the type of acupuncture performed in this study. The acupuncture performed was based on Jin's three needle theory (JTN) and, while it has been used for several decades for treatment of mental illnesses, it has previously not been investigated in the management of opioid use disorder. Due to its effectiveness in improving symptoms of depression and anxiety, Jin's three needle theory was used in this study.

As stated earlier, the majority of studies examining the effectiveness of acupuncture as an adjunctive treatment have been conducted in China, which could introduce potential bias considering acupuncture's long-standing integration into Traditional Chinese Medicine (TCM). Moreover, generalizing their findings to Western societies, particularly the United States, is challenging due to inherent cultural and societal differences. There is a gap in research within the United States that needs to be addressed, in order to determine the effectiveness of acupuncture as an adjunctive therapy for opioid use disorder. Given that insurance companies are now including acupuncture

as part of conservative management strategies, it is crucial to investigate whether acupuncture offers more than a placebo effect and whether it can truly contribute to curbing the opioid epidemic, thereby alleviating the psychological and economic burden to our healthcare system.

METHODS

Study design

The study will be a randomized, single-blind trial aiming to demonstrate the efficacy of acupuncture as an adjunctive therapy for patients undergoing MMT. Prior to randomization, all participants will provide informed written consent to participate in the study. The population will consist of 140 eligible participants that will be randomly assigned to an experimental (n = 70) and control group (n = 70) after enrollment, in a 1:1 ratio, with participants blinded to their assignment. Randomization will be determined by a random number table generated by a computer and managed by an independent researcher. The experimental group will receive MMT and true acupuncture, while the control group will receive MMT and sham acupuncture, which involves the use of placebo or double-blind needles. Due to the nature of the intervention, acupuncturists cannot be blinded, resulting in a single-blind study. However, participants, independent researchers, and statisticians will remain blinded throughout the study.

The study will be conducted over a six-week experimental period, followed by a three-month follow-up period. The primary outcome measures will include methadone dosages measured at baseline, second, fourth, and sixth week, as well as the VAS scale. The secondary outcome measure will include urine drug screening tests and the SF-36 scale. Before the experiment begins, participants will undergo an evaluation consisting of urine drug screening and calculation of their baseline methadone dosages. Additionally, they will complete the VAS and SF-36 surveys, which will be used for

comparison from baseline to the end of the experiment. This evaluation will be conducted by an independent researcher.

Two acupuncturists will be selected based on specific qualifications, including a masters or doctoral level degree in acupuncture accredited by organizations such as the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM), Accreditation Commission for Acupuncture and Herbal Medicine (ACAHM), or American College of Acupuncture and Oriental Medicine (ACAOM). In addition, they must have more than three years of experience performing acupuncture in a clinical setting.

Study population and sampling

The study population will be selected from the Comprehensive Treatment Clinics associated with Boston Medical Center. There are four primary locations that will be targeted: Boston, Lynn, Brockton, and Lowell. Subjects will have an official diagnosis of opioid use disorder, as stated in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V).

Table 1 provides a comprehensive overview of inclusion and exclusion criteria used in the study. The study includes adult patients between the ages of 18-60 years old that were able to sign an informed consent. The inclusion criteria for this study require patients who have been actively attending a methadone clinic for more than thirty days. This criterion ensures the inclusion of individuals who have had sufficient time to adapt to their methadone dosage and treatment regimen. Since sham acupuncture uses a

superficial technique, in which needles are not penetrated as deeply into the skin, the inclusion criteria for the study includes patients who have not been previously subjected to any type of acupuncture therapy, so they would not be accustomed to the sensation of how deep the acupuncture needles should penetrate their skin.

Since acupuncture is considered a relatively safe procedure and has been previously used in vulnerable populations, such as pregnant women and pediatric patients, without adverse effects, there are few absolute contraindications. Therefore, the study's exclusion criteria focus on selecting a patient population that ensures the safest and most effective treatment outcomes. Exclusion criteria encompass patients with mechanical heart valves or pacemakers, as there can be potential electromagnetic interference and an increased risk of infection in these cases. Patients with existing cutaneous infection, HIV, or malignancy are also excluded to prevent the spread of infection or neoplastic cells through the use of needles. Furthermore, patients with bleeding disorders and those on anticoagulation therapy are excluded due to increased risk of bleeding. Patients with a history of strokes accompanied by residual weakness or hemiballismus, as well as those with underlying movement disorders, such as benign tremors, Parkinson's Disease, or Huntington's Disease, are also excluded. Their unpredictable movements may lead to needle misplacement, posing a higher risk of adverse outcomes.

Patients who have relapsed within the past three months or have concurrent cocaine or amphetamine use, as indicated by the urine drug screen, are excluded from the study. Since these patients would not benefit from methadone maintenance trial, the

study would not effectively determine the potential adjunctive use of acupuncture with MMT. Cannabis use is not included in the exclusion criteria as marijuana is legalized in Massachusetts. Considering the absence of political barriers to cannabis use in Massachusetts, urine drug screens positive for cannabis are included.

In many acupuncture studies, populations with psychiatric co-morbidities are often excluded. However, it was not feasible for the current study to exclude individuals with psychiatric co-morbidities, as the diagnosis of opioid use disorder frequently co-occurs with various psychiatric conditions. Additionally, it is possible that acupuncture could have a positive impact on symptoms of depression and anxiety, given the overlap and interconnectedness of these symptoms with the psychological aspects of opioid use and addiction.

The sample size and power calculation for this study were based on a study conducted by Wen et al. in 2020. In their study, VAS was used as the primary measure to assess drug craving. Previous research allowed them to determine that the difference in VAS scores between baseline and endpoint was approximately 37.5 +/- 28 for the true acupuncture group and 20 +/- 30 for the sham acupuncture group. By applying the same mean difference values, along with a power of 90%, an alpha level of 5%, and an estimated dropout rate of 15%, a sample size of 140 participants was calculated. This results in an allocation of 70 subjects to both the experimental and control groups.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
1. Male or female
2. 18-60 years old
3. Are able to sign the informed consent
4. Have been attending the Methadone Clinic for > 30 days
5. Have previously not been subjected to any type of acupuncture therapy

Exclusion Criteria
1. Mechanical heart valves or pacemakers
2. Active infections or malignancy
3. HIV positive
4. On anticoagulant therapy or history of bleeding disorders
5. Previous history of stroke or psychiatric disorder presenting with residual movement disorders, resulting in uncontrolled movements
6. Severe phobia or extreme anxiety with needle use
7. Reported or prior positive urine study for concomitant illicit drug use, including cocaine or amphetamine use within the past three months (except those with diagnosis of ADHD or similar disorder, requiring the use of amphetamines for daily use
8. Pregnant patients ‘

Treatment (or intervention)

Two groups will be randomly allocated after enrollment with each group consisting of 70 participants. The interventional or experimental group will receive acupuncture in addition to their MMT and the control group will receive sham acupuncture in addition to their MMT. Acupuncturists will perform sessions three times

a week for a total of six weeks, resulting in eighteen sessions. These treatments will be conducted in a quiet treatment room at Boston Medical Center. Two acupuncturists will be selected based on their accreditation and clinical experience and each subject will have the same acupuncturist for all treatment sessions.

The selection of acupoints and needle placement techniques in this study was based on research conducted by Wen et al. at Guangzhou Huiai Hospital. They utilized acupoint groups known as *Dingshen-zhen*, *Sishen-zhen*, and *Shouzhi-zhen* (Figure 2), according to Jin's three-needle theory. The *Dingshen-zhen* group consisted of three acupoints, the *Sishen-zhen* group had four acupoints, and the *Shouzhi-zhen* group included three points. During each session, ten sterile stainless steel disposable acupuncture needles were applied to the patients and left in place for a duration of thirty minutes.

Following established acupuncture protocols, the *Dingshen-zhen* and *Sishen-zhen* groups had needles inserted at an angle of 15-30° to the skin, while the *Shouzhi-zhen* group had needles placed at an angle of 45-90°. The depth of each needle insertion ranged from 5-30 mm. In the control group, the same methodology was employed, using double-blind needles that did not penetrate the skin. The position, angle, and duration of needle placement remained consistent across both groups. The acupuncturists selected for this study were experienced and knowledgeable in these specific acupoints as well as skilled in eliciting *de qi*, the acupuncture sensation of soreness, numbness, or distension associated with needle stimulation.

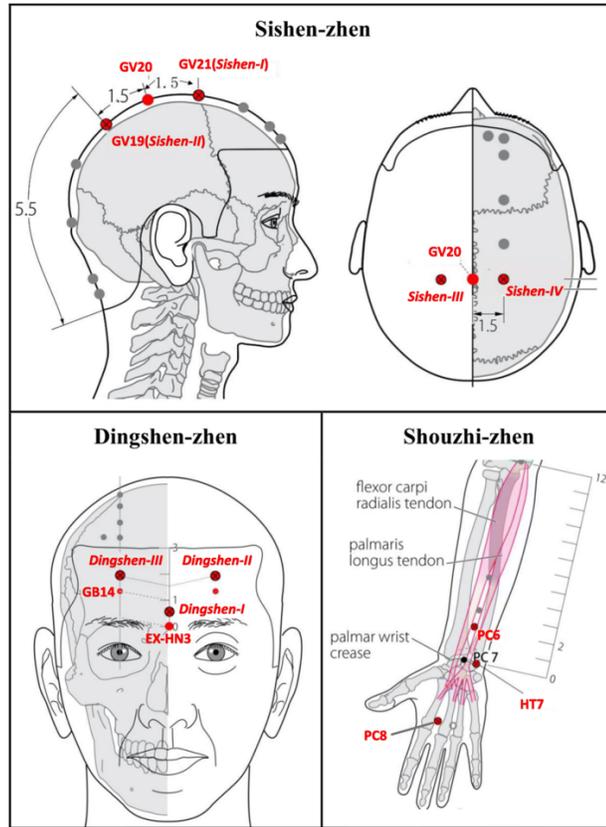


Figure 2: Acupoints: Dingshen-zhen, Sishen-zhen, and Shouzi-zhen

Study variables and measures

Two primary outcomes will be utilized in the study: (1) methadone dosage and (2) VAS score for drug craving. Prior to the start of the experiment, patients' baseline methadone dosage will be documented. Subsequent measurements of methadone dosage will be taken at weeks 2, 4, and 6 during the experimental period. Additionally, during the three-month follow-up period, methadone dosage will be measured at weeks 8, 10, 12, 14, 16, and 18. Adjustments in methadone dosage will be made by a physician, who will rely on clinical judgement and experience to make informed decisions. The VAS scale is used to assess drug craving, which will be the second primary outcome measured. Participants will be provided with a 100-mm line and asked to rate their level of craving on a scale of 0 (no craving) to 100 (strong craving). The administration of the VAS scale will follow the same schedule as the methadone dosage measurements so that patients are able to record their craving scales every other week.

The secondary outcomes measured in this study include: (1) urine drug screening tests and (2) quality-of-life survey measured via the Short-Form Survey (SF-36, included in the Appendix), which consists of 36 questions. Urine drug screens will be conducted weekly, following the completion of the last acupuncture session for the week. The SF-36 will be given to patients on weeks 2, 4, 6 during the experimental period and weeks 8, 10, 12, 14, 16, and 18 during the three-month follow-up period. This is a series of questions that utilizes eight domains to assess the patient's quality of life. These domains include: (1) physical functioning (PH), used to assess a patient's ability to perform activities of daily living; (2) role-physical, used to assess the individual's physical health status and how this affects their ability to carry out daily tasks; (3) bodily pain, used to assess the individual's perception of pain and its impact on their overall well-being and daily activities; (4) general health, used to assess the patient's perception of their overall health; (5) vitality, used to assess the patient's energy levels and overall sense of well-being; (6) social functioning, used to assess the patient's ability to participate in social activities and their perception of social interactions and support; (7) role-emotional, used to assess the patient's emotional and mental health and how this impacts their ability to carry out daily activities of living; and (8) mental-health, used to assess the patient's psychological well-being, including aspects such as mood, anxiety, and depression.

Recruitment

Patients will be recruited through various methods at the Boston Comprehensive Treatment Center, which is affiliated with Boston Medical Center. The

recruitment process will take place simultaneously across all four locations: Boston, Lynn, Brockton, and Lowell. In addition to advertisements and flyers placed in clinic, referrals from healthcare providers from the treatment centers will also occur. To be eligible for the study, patients must meet specific criteria. Once individuals' express interest and provide written consent to participate, an evaluation will be conducted by an independent researcher. This evaluation will determine study eligibility and gather important baseline information, including demographic data and details about their methadone usage, VAS, and responses to the SF-36. During this process, patients will be given a general summary of the experimental process and will be given an opportunity to ask questions and seek clarifications before proceeding further.

Data collection

Relevant data will be collected in case report forms (CRFs) by independent trained researchers, who are not involved in the study. These researchers will be responsible for collecting all data from the healthcare personnel, including the dosages of methadone used, the results of the urine drug screen, and/or any adverse outcomes related to acupuncture use. The VAS and SF-36 surveys will be conducted by these researchers. The data will be recorded in CRFs and entered into a password-protected computer system. Once all data has been collected and the study has concluded with its six-week experimental period and three-month follow up period, the data will be analyzed by statisticians that are independent to the study.

Data analysis

The analysis of the data will be performed with both the intention-to-treat (ITT) principle and per-protocol (PP) analysis. The ITT analysis includes all participants that were originally included in the study, regardless of their adherence or completion of the protocol. The PP analysis focuses on only participants that have adhered to the criteria outlined in the study and completed the treatment protocol. Utilizing both analyses will provide us with a more thorough understanding of research findings. Missing data will be replaced by principle of multiple imputations.

Mean change will be represented by descriptive statistics, including standard deviation and 95% confidence interval. Statistical significance will be defined as p vales < 0.05 . Baseline characteristics and demographic data will be collected and analyzed using analysis of variance (ANOVA) or chi-square test as appropriate. The independent samples t-test will be employed to compare means between the experimental and control groups. Additionally, a two-way ANOVA will be conducted to assess the interaction between time and treatment. All statistical analyses will be performed by an independent and trained statistician.

Timeline and resources

A previous study conducted at Guangzhou Hui'ai Hospital by Wen et al had a recruitment process lasting approximately one year from October 2019 to September 2020. The intervention phase required an additional six weeks, followed by a three-

month follow-up weekly participant visits. The entire duration of the experiment is estimated to be around one and a half years. The subsequent statistical analysis is anticipated to take approximately one to two months. To account for potential challenges and contingencies that may occur during the study, a total of two years will be allocated for the entire protocol.

The financial costs of the study will include the location where acupuncture session will be performed, the recruitment flyers, which will be distributed across various locations of the Comprehensive Treatment centers. Additionally, costs will be incurred for the acupuncturists hired to administer the treatments, the necessary medical equipment for weekly urinalysis studies, the medical staff responsible for evaluating appropriate methadone dosages, the researchers collecting data, and the independent statistician required for data analysis.

Institutional Review Board

As this study involves an economically disadvantaged population and includes collection of information about highly sensitive topics and, possibly, illegal behavior, this study warrants a Full Review by the Institutional Review Board (IRB). The study will be submitted to Boston University Medical Center and reviewed under INSPIR II.

CONCLUSION

Discussion

The opioid epidemic has remained at the forefront of public health for several years with the fourth wave of the epidemic occurring as a result of the introduction of fentanyl. As the opioid epidemic continues to present a challenge in the United States, new alternatives for management may be desirable in the foreseeable future with acupuncture presenting as a possible viable adjunctive therapy due to its ability to elicit an analgesic effect. Based on previous studies, it is unclear whether acupuncture can decrease the use of opioids in patients with opioid use disorder, however, recent studies performed in China have shown promising results. The study highlighted in this paper models a recent study performed at Gangzhou University, where acupuncture was performed in patients placed on methadone maintenance programs with favorable results indicating a decreased dose of methadone required with adjunctive acupuncture.

The aim of the study designed in this paper is to investigate the potential benefits of acupuncture as an adjunctive therapy to methadone maintenance treatment for patients with opioid use disorder (OUD). The study design involves a randomized double-blind approach with subjects assigned to either the control group (receiving sham acupuncture and MMT) or the experimental group (receiving real acupuncture and MMT). The study population will be selected from Comprehensive Treatment Clinics associated with Boston Medical Center, consisting of individuals diagnosed with OUD according to the DSM-V criteria. There are two primary outcome measures - the weekly dose of methadone required and the VAS for drug craving. These measurements will provide

insights into the effectiveness of acupuncture as an adjunctive therapy. In addition, secondary outcomes include urine drug screening tests and the SF-36 to assess the participants' quality of life.

While the hypothesis is that this study will produce similar results, the experimental design created does have several limitations. The study is conducted at Comprehensive Treatment Clinics associated with Boston Medical Center, which may limit the generalizability to other populations or geographic locations. In addition, this study relies on recruiting participants from Comprehensive Treatment Clinics, which may introduce selection bias. The patient population in these clinics may differ from the broader population of individuals with opioid use disorder, potentially affecting the external validity of the findings. In addition, patients receiving medication at the methadone clinic are intrinsically motivated to seek treatment for their diagnosis of opioid use disorder, resulting in further bias. The exclusion criteria also limits the generalizability of the study. Excluding patients with certain medical conditions or recent substance use may eliminate a portion of the population that would benefit from the intervention. Many patients diagnosed with opioid use disorder have co-morbidities that can potentially exclude them from the study, raising this as an ethical concern. These patients may have easier access to treatment, as the study resides in an urban setting, whereas patients in other parts of the country or those residing in a rural setting may not have the same resources with difficulty traveling to methadone clinics. Moreover, only those patients that can attend methadone clinic everyday have been included in the study, as methadone is a controlled substance. There is also self-reporting

bias within the study, as some of the outcome measures, such as the Visual Analogue Scale (VAS) for drug craving and the Short-Form Survey (SF-36) for quality of life, rely on self-reporting by the participants. This introduces the potential for response bias, as patients may provide socially desirable answers or overstate any improvements they may feel.

Blinding challenges must also be acknowledged. While efforts have been made to maintain blinding by using placebo needles, it is possible that participants and acupuncturists may be able to discern whether they are receiving real or sham acupuncture. This could introduce performance bias or expectations that may influence participant responses. There may also be participants in both groups that may experience a psychological response or expect improvements due to their participation in the study, potentially resulting in placebo effects and influencing the results of the study.

Additionally, the study involves patients within the Boston area with opioid use disorder who are at a higher disadvantage of being at a lower socioeconomic background with unstable housing. Due to the lack of stability in these patients' lives, a high dropout rate is likely in the study. While a 15% drop-out rate was accounted for in sample size calculations, the number may be higher when taking into account the commitment needed to attend acupuncture sessions and undergo multiple evaluations.

While the study does have limitations in its design, it may be an appropriate starting point to begin researching the use of alternative adjunctive therapeutic options for opioid use disorder. With the rising public health concerns and the increasing economic burden of opioid use, any means to curb its growth should be explored. Since

acupuncture has very low risk of adverse effects, it may be a safe and efficacious options for patients with OUD.

Summary

The use of both prescription and illicit opioids has markedly increased in the past several decades worldwide. In the United States, opioid use disorder presents a significant economic burden within our healthcare system. Opioids have been used widely throughout history due to their analgesic and euphoric properties. Because of their high addictive potential, patients previously prescribed opioids for chronic pain syndrome and other co-morbidities have had increased dependence and tolerance on these medications. With the advent of new guidelines and federal regulations, prescription of medications in the opioid class have been under increasing scrutiny. With these changes, there has been increased use of illicit drugs, as these are more readily available for those already reliant on opioids. However, illicit drugs are often laced with other substances that increase their addictive potential, including fentanyl. Due to these changes, there has been a marked increase in opioid associated overdose and deaths, resulting in the United States entering the fourth wave of the epidemic.

In response to this, insurance companies have made changes in conservative guidelines for patients requiring opioids for pain management. In particular, there has been interest in investigating alternative therapies, including acupuncture. Acupuncture has long been used in Chinese Medicine and has been incorporated in Western society with uses in pain management, especially for migraines, fibromyalgia, and osteoarthritis.

Physiologically, acupuncture has been noted to elicit an analgesic response by stimulating various points in the body, corresponding to specific fields within the meridian system that result in activation and release of endogenous opioids, thereby resulting in reduction of pain. While acupuncture has been noted to lead to an improvement in the management of pain, the use of acupuncture in opioid use disorder has not been greatly explored. Studies have previously been conducted that elucidate the effectiveness of acupuncture combined with opioids in reducing pain, however, there have been few studies that highlight the role of acupuncture in patients receiving medication assisted therapy for treatment of opioid use disorder and whether the use of acupuncture caused a decrease in relapses amongst patients. Previous studies have either failed to show a significant difference or found inconclusive results. It's important to note that the studies that failed to show a significant difference either used sample sizes that were too small or conducted the study for a very short period. A recent study conducted in China indicated the efficacy of acupuncture as an adjunctive treatment to methadone use. In this study, there was a decrease in methadone use and a decrease in relapse rate of patients who were receiving true acupuncture in addition to methadone. While the study seemed promising, due to its population residing in Guangzhou Huiai Hospital, its generalizability was limited, as the demographics and culture in the United States differs from that of China. Therefore, performing a similar study in the United States will be beneficial to investigate the benefits of acupuncture use.

The experimental design proposed in this paper utilizes a population from Boston that has been diagnosed with opioid use disorder, as diagnosed by DSM-V. These

patients will be receiving methadone maintenance treatment in addition to true acupuncture or sham acupuncture for a six-week period, consisting of three sessions weekly for a total of eighteen sessions. During the experiment, primary outcomes of methadone use and scores on the VAS scale will be collected, as well as secondary outcomes of urinary drug screening tests and SF-36 scores. The hypothesis remains that the use of true acupuncture will result in a decrease in methadone dosage, a decrease in relapse, and an overall improved quality of life, as indicated by the SF-36 score.

Clinical and/or public health significance

The opioid epidemic has affected a large portion of the population, cutting across various demographic groups and geographic regions. It has led to a substantial increase in opioid-related overdoses, deaths, and substance use disorders, devastating individuals and communities. Prescription opioids, such as oxycodone and hydrocodone, as well as illicit opioids, like heroin, and synthetic opioids, like fentanyl, have contributed to a sharp rise in overdose fatalities, resulting in the United States entering the fourth wave of the opioid epidemic. The high mortality rates associated with this misuse makes it a pressing public health concern and places a significant economic burden on society. Costs arise from healthcare expenditures, including emergency room visits, substance abuse treatment, rehabilitation programs, and medical interventions for overdose cases. In addition, the use of needles contributes to the spread of infectious diseases, such as HIV and hepatitis, further increasing demand and straining our resources. Due to its multifaceted impact, the opioid epidemic is recognized as a public health crisis,

necessitating a comprehensive and coordinated response from healthcare providers, policymakers, law enforcement agencies, community organizers, and individuals to address its devastating effects on individuals, families, and society.

The impact of discovering alternative therapies to opioid use should not be undermined. Acupuncture has long been shown to have potential in managing pain, reducing opioid cravings, and alleviating withdrawal symptoms in individuals with opioid use disorder. Investigating its effectiveness as an adjunct to methadone maintenance therapy can provide valuable insight into its clinical benefits and contribute to improved patient outcomes. If acupuncture is found to be effective in reducing opioid cravings and withdrawal symptoms, it could potentially lead to lower methadone dosage requirements. This could benefit patients by reducing their dependence on medication, minimizing associated side effects, and providing alternative treatment options.

The opioid crisis is a significant public health concern globally. Exploring adjunctive therapies like acupuncture can help expand the range of treatment options available, potentially reducing the burden on opioid-based medications. This research may contribute to a more comprehensive and diversified approach to managing opioid use disorder.

APPENDIX

Short-Form Survey 36

General Health:

1. In general, would you say your health is:
 - a. Excellent
 - b. Very good
 - c. Good
 - d. Fair
 - e. Poor

2. Compared to one year ago, how would you rate your health in general now?
 - a. Much better now than one year ago
 - b. Somewhat better than one year ago
 - c. About the same
 - d. Somewhat worse now than one year ago
 - e. Much worse than one year ago

Limitations of Activities:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

1. Vigorous activities, such as running, lifting, heavy objects, participating in strenuous sports.
 - a. Yes, limited a lot

- b. Yes, limited a little
 - c. No, not limited at all
- 2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf
 - a. Yes, limited a lot
 - b. Yes, limited a little
 - c. No, not limited at all
- 3. Lifting or carrying groceries
 - a. Yes, limited a lot
 - b. Yes, limited a little
 - c. No, not limited at all
- 4. Climbing several flights of stairs
 - a. Yes, limited a lot
 - b. Yes, limited a little
 - c. No, not limited at all
- 5. Climbing one flight of stairs
 - a. Yes, limited a lot
 - b. Yes, limited a little
 - c. No, not limited at all
- 6. Bending, kneeling, or stooping
 - a. Yes, limited a lot
 - b. Yes, limited a little

- c. No, not limited at all
- 7. Walking more than a mile
 - a. Yes, limited a lot
 - b. Yes, limited a little
 - c. No, not limited at all
- 8. Walking several blocks
 - a. Yes, limited a lot
 - b. Yes, limited a little
 - c. No, not limited at all
- 9. Walking one block
 - a. Yes, limited a lot
 - b. Yes, limited a little
 - c. No, not limited at all
- 10. Bathing or dressing yourself
 - a. Yes, limited a lot
 - b. Yes, limited a little
 - c. No, not limited at all

Physical Health Problems:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

- 1. Cut down the amount of time you spent on work or other activities
 - a. Yes

- b. No
- 2. Accomplished less than you would like
 - a. Yes
 - b. No
- 3. Were limited in the kind of work or other activities
 - a. Yes
 - b. No
- 4. Had difficulty performing the work or other activities (for example, it took extra effort)
 - a. Yes
 - b. No

Emotional Health Problems:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

- 1. Cut down the amount of time you spent on work or other activities
 - a. Yes
 - b. No
- 2. Accomplished less than you would like
 - a. Yes
 - b. No
- 3. Didn't do work or other activities as carefully as usual

- a. Yes
- b. No

Social Activities:

1. Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
 - a. Not at all
 - b. Slightly
 - c. Moderately
 - d. Severe
 - e. Very severe

Pain:

1. How much bodily pain have you had during the past 4 weeks?
 - a. None
 - b. Very mild
 - c. Mild
 - d. Moderate
 - e. Severe
 - f. Very severe
2. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
 - a. Not at all
 - b. A little bit

- c. Moderately
- d. Quite a bit
- e. Extremely

Energy and Emotions:

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

1. Did you feel full of pep?
 - a. All of the time
 - b. Most of the time
 - c. A good bit of the time
 - d. Some of the time
 - e. A little bit of the time
 - f. None of the time
2. Have you been a very nervous person?
 - a. All of the time
 - b. Most of the time
 - c. A good bit of the time
 - d. Some of the time
 - e. A little bit of the time
 - f. None of the time
3. Have you felt so down in the dumps that nothing could cheer you up?

- a. All of the time
 - b. Most of the time
 - c. A good bit of the time
 - d. Some of the time
 - e. A little bit of the time
 - f. None of the time
4. Have you felt calm and peaceful?
- a. All of the time
 - b. Most of the time
 - c. A good bit of the time
 - d. Some of the time
 - e. A little bit of the time
 - f. None of the time
5. Did you have a lot of energy?
- a. All of the time
 - b. Most of the time
 - c. A good bit of the time
 - d. Some of the time
 - e. A little bit of the time
 - f. None of the time
6. Have you felt downhearted and blue?
- a. All of the time

- b. Most of the time
- c. A good bit of the time
- d. Some of the time
- e. A little bit of the time
- f. None of the time

7. Did you feel worn out?

- a. All of the time
- b. Most of the time
- c. A good bit of the time
- d. Some of the time
- e. A little bit of the time
- f. None of the time

8. Have you been a happy person?

- a. All of the time
- b. Most of the time
- c. A good bit of the time
- d. Some of the time
- e. A little bit of the time
- f. None of the time

9. Did you feel tired?

- a. All of the time
- b. Most of the time

- c. A good bit of the time
- d. Some of the time
- e. A little bit of the time
- f. None of the time

Social Activities:

1. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?
 - a. All of the time
 - b. Most of the time
 - c. Some of the time
 - d. A little bit of the time
 - e. None of the time

General Health:

How true or false is each of the following statements for you?

1. I seem to get sick a little easier than other people
 - a. Definitely true
 - b. Mostly true
 - c. Don't know
 - d. Mostly false
 - e. Definitely false
2. I am as healthy as anybody I know

- a. Definitely true
- b. Mostly true
- c. Don't know
- d. Mostly false
- e. Definitely false

3. I expect my health to get worse

- a. Definitely true
- b. Mostly true
- c. Don't know
- d. Mostly false
- e. Definitely false

4. My health is excellent

- a. Definitely true
- b. Mostly true
- c. Don't know
- d. Mostly false
- e. Definitely false

LIST OF JOURNAL ABBREVIATIONS

Acta Pharm Hung	Acta Pharmaceutica Hungarica
Annu Rev Med	Annual Review of Medicine
Biomed J	Biomedical Journal
Biomed Pharmacother	Biomedicine & Pharmacotherapy
Civ War Hist	Civil War History
Curr Opin Neurobiol	Current Opinion in Neurobiology
Curr Opin Psychiatry	Current Opinion in Psychiatry
Drug Alcohol Depend	Drug and Alcohol Dependence
Front Neurosci	Frontiers in Neuroscience
Int J Drug Policy	International Journal on Drug Policy
Int J Mol Sci	International journal of Molecular Sciences
J Acupunct Meridian Stud	Journal of Acupuncture and Meridian Studies
J Integr Med	Journal of Integrative Medicine
J King Abdulaziz Univ Med Sci	Journal of King Abdulaziz University: Medical Sciences
J Neurol	Journal of Neurology
J Subst Abuse Treat	Journal of Substance Abuse Treatment
JAMA	JAMA: The Journal of the American Medical Association
JAMA Netw Open	JAMA Network Open
Mol Psychiatry	Molecular Psychiatry
Neurosci Biobehav Rev	Neuroscience and Biobehavioral Reviews
Pain Ther	Pain and Therapy
Prev Med	Preventive Medicine

Psychol Trauma Theory Res Pract
Policy

Q J Econ

Sci Pract Perspect

Semin Perinatol

Subst Abuse

Psychological Trauma: Theory, Research,
Practice and Policy

Quarterly Journal of Economics

Science & Practice Perspectives

Seminars in Perinatology

Substance Abuse

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