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Evidence Brief: The Comparative Effectiveness of Selected Complementary and Integrative Health (CIH) Interventions for Preventing or Reducing Opioid Use in Adults with Chronic Neck, Low Back, and Large Joint Pain

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

· Develop clinical policies informed by evidence;
· Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
· Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces "rapid response evidence briefs" at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

Over the past 2 decades, there has been a dramatic increase in opioid-related overdose deaths, dependence, and misuse. As a result, there is intense interest in non-opioid alternatives for treating chronic pain. Select Complementary and Integrative Health (CIH) interventions may be a reasonable non-opioid treatment option in general, if they can improve pain at a magnitude comparable to opioids, but without serious side effects. Whether CIH interventions can reduce chronic opioid use is of great interest in the fight against the opioid epidemic.

The evidence base regarding the effectiveness of select CIH interventions for reducing opioid use is extremely limited. No study has evaluated the effectiveness of select CIH interventions for reducing new opioid use, stopping opioids entirely, or for reducing opioid use below any particular morphine equivalent dose (MED) threshold. Compared to sham, in patients already using a dosage below 80 mg MED, there is low-strength evidence that certain electro-acupuncture modalities can reduce opioid dose after 6 to 10 weeks of treatment. This was found both in a group of Australian patients with various forms of chronic pain undergoing a planned opioid tapering and in a group of Veterans with advanced knee osteoarthritis taking opioids for an unknown duration. But these effects were not sustained 5-9 months following acupuncture discontinuation (Table ES1). Single studies of massage, meditation, and yoga provided insufficient evidence to draw conclusions about their effects on opioid dose because (1) they lacked details about opioid type, dose, and frequency and (2) relied on self-assessments from unblinded patients, with no effort to match the intervention to a sham treatment group, which could have led to more favorable assessments in the experimental groups. We found no studies that evaluated the impact of tai chi or classic acupuncture on opioid use.

Additional research is needed to better understand the effectiveness of select CIH interventions for reducing opioid use in Veterans. To best remedy key limitations of current evidence, future research should seek to: (1) evaluate the most clinically relevant outcomes of reducing new use, stopping opioids entirely, and/or reducing opioid use below relevant MED threshold(s) using suggested measurement methods, (2) simultaneously measure a complete set of key outcomes, including impact on pain, pain-related function, quality of life, and harms, including potential consequences of reducing opioid use, (3) clarify whether the effectiveness of CIH varies depending on the timing of their integration, and (4) identify particular subpopulations that are more or less likely to benefit from CIH to reduce opioid use and whether variation in benefit varies by CIH type.

Background

To inform VA's research initiative to evaluate non-opioid alternative approaches to pain management, its Health Services Research and Development Service (HSR&D) is planning a state-of-the-art (SOTA) conference for November 2016 to help define future directions of research for all non-opioid alternative approaches to pain management. To inform their interim April 2016 Expert SOTA Planning Meeting, HSR&D commissioned the Evidence-based Synthesis Program Coordinating Center (ESP CC) to conduct an evidence brief on the effectiveness of select Complementary and Integrative Health (CIH) interventions (*ie*, acupuncture, massage, meditation, tai chi, and yoga) for reducing opioid use in adults with chronic neck, low back, and large joint pain.

Methods

To identify studies, we reviewed bibliographies from recent good-quality systematic reviews and supplemented this with a Medline search for more recent studies. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See our PROSPERO protocol for our full methods.

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Evidence-based Synthesis Program

Table ES1. Characteristics and Findings of Acupuncture Studies

Author Year Risk of Bias N Pain type	Interventions	Opioid type and dose	Impact on opioid use	Pain, quality of life, functional status, adverse events
Sator-Katzenschlager 2004 [1] Unclear N = 61 LBP	Auricular acupuncture with electrical stimulation (EA) or without stimulation (CO)	Tramadol ≤ 400 mg daily	EA reduced # opioid tablets consumed throughout intervention: EA = 6 vs CO = 150 ($P < .001$)	EA reduced pain (10-point VAS scale) at 18 wks: EA = 1 vs CO = 4 ($P < 0.05$) EA reduced well-being impairment (10-point VAS scale) at 18 wks: EA = 1 vs CO = 5 ($P < 0.05$) Adverse events: none observed
Weiner 2013 [2] Unclear N = 190 Veterans with Knee OA	Periosteal stimulation therapy, with boosters (PST+PST) or without boosters (PST+control) or control PST without boosters (control)	Opioid type NR: average 0.47 doses/wk	Opioid consumption at 10 wks PST+PST similar to Control PST: 0.018 (95% CI -0.19 to 0.23) PST+control reduced consumption vs Control PST : -0.27 (95% CI -0.48 to -0.054)	9 m outcomes: PST+PST improved WOMAC pain (MD 1.5, 95% CI 0.069 to 3.0), but not SF-36 physical component (MD -1.2; 95% CI -2.8 to 0.041) vs Control PST PST+control did not improve WOMAC pain (MD 1.1, 95% CI -.32 to 2.6) or SF-36 physical component (MD -1.3; 95% CI -3.0 to 0.28) vs Control
Zheng 2008 [3] Unclear N = 35 NMCP	Electroacupuncture (REA) or sham electroacupuncture (SEA)	Codeine, Methadone, Oxycodone, Morphine, & Tramadol Dose (mg/d morphine equivalent): REA = 65.9/d SEA = 42.2/d	REA reduced OLM consumption (change from baseline, mg/d morphine equivalent) at 8 wks: REA = -25.7 vs SEA = -10.9 20 wks: REA = -16.7 vs SEA = -8.1	REA reduced pain (scale NR): Change from baseline at 8 wks: -0.8 REA vs -0.7 SEA ($P = .001$) Adverse events: 33 events REA and 19 events SEA

EA: Auricular acupuncture with electrical stimulation; CO: Auricular acupuncture without electrical stimulation; PST: Periosteal stimulation therapy; LBP: Low back pain; VAS: Visual Analog Scale; OA: Osteoarthritis; WOMAC: Western Ontario & McMaster Universities Osteoarthritis Index Evidence Brief; NMCP: Non-malignant chronic pain; REA: Electroacupuncture; SEA: Sham electroacupuncture; OLM: Opioid-like medications; NR: Not reported

INTRODUCTION

PURPOSE

In October, 2015, the White House announced that the VA would lead an initiative to evaluate non-opioid alternative approaches to pain management. [https://www.whitehouse.gov/the-press-office/2015/10/21/fact-sheet-obama-administration-announces-public-and-private-sector] To inform this initiative, the VA Health Services Research and Development Service (HSR&D) is planning a state-of-the-art (SOTA) conference for November 2016 to help define the future directions of research for all non-opioid alternative approaches to pain management. In April 2016, HSR&D will convene an Expert SOTA Planning Meeting, and commissioned the Evidence-based Synthesis Program Coordinating Center (ESP CC) to conduct an evidence brief on select Complementary and Integrative Health (CIH) interventions to inform that meeting.

Key goals of the April planning meeting are to identify: (1) preliminary consensus policy conclusions based on what is known about CIH approaches to reduce opioid use, (2) preliminary gaps in evidence, (3) a research agenda for National Center for Complementary and Integrative Health (NCCIIH)/Department of Veterans Affairs (VA)/Department of Defense (DOD) collaboration for CIH approaches to pain management and comorbidities, and (4) key questions for more in-depth examination at the November 2016 SOTA. For the November 2016 SOTA, additional work will be done to evaluate all non-pharmacological approaches, including cognitive behavioral therapy (CBT) and additional key outcomes, including pain, function, PTSD, sleep, and quality of life.

BACKGROUND

The Opioid Overdose Epidemic

Opioid analgesics are a class of prescription medications (morphine, hydrocodone, oxycodone, *etc*) that the FDA has classified as controlled substances (Schedule 2 drug) due to their high potential for abuse and dependence. Between 1999 and 2011, the United States saw a 319% increase in deaths due to prescription opioid analgesic-related overdoses. Because this increase far exceeded that for deaths due to heroin (+149%) and cocaine (+22%) and it outnumbered motor vehicle crash and gunshot-related deaths,[4] in 2012 the CDC characterized the problem as an epidemic.[5] Compared to the general US population, VHA patients may have an elevated risk of death due to prescription opioid overdose (crude rate per 100,000 person-years = 1.96 vs 10.49; standardized mortality ratio 1.96, 95% CI 1.83 to 2.08).[6]

The increase in opioid prescribing that began in the late 1990s is frequently cited as a key determinant of increased opioid-related overdose mortality.[7] The causes of increased prescribing have been widely debated and are likely numerous. Recent data from 3 large health care systems, including the VHA, have shown that higher doses are a risk factor for prescription opioid overdose deaths[8-10] and suicide.[11] Among Veterans taking opioids for pain, compared to those prescribed a Morphine Equivalent Dose (MED) of < 20 mg, risk of death increased for MED 20 to < 50 mg (HR 1.88; 95% CI 1.33 to 2.67), 50 to < 100 mg (HR 4.63, 95% CI 3.18 to 6.74), and ≥ 100 mg (HR 7.18; 95% CI 4.85 to 10.65).[10] Studies examining the association between opioid dose and death have categorized dose in a variety of ways for a variety of reasons, but evidence has not yet identified a clear dose "threshold" for overdose risk.[12] Rather, evidence seems to

suggest that risk increases as dose increases, starting with very low doses. The new CDC guidelines recommend additional caution at 50 mg and avoidance of prescribing > 90 mg, but acknowledge that there is no threshold for risk.[13]

Many factors contribute to opioid-related mortality. A systematic review identified 3 categories of potential determinants of increased opioid-related mortality in the United States and Canada from 1990 to 2013[14]: (1) *Prescriber behaviors*: increased prescriptions and sales of opioids, prescribing higher doses of opioids, prescribing oxycodone, prescribing methadone, and prescribing at high volumes, (2) *User behavior and characteristics*: history of substance abuse, diversion, doctor or pharmacy shopping, drug substitution, polydrug toxicity, sociodemographic characteristics (men, non-Hispanic Whites and American Indian/Alaska Natives, middle-aged individuals, those living in rural areas, and those of lower socioeconomic status), and (3) *Environmental and systemic determinants*: area urbanization or socioeconomic status, geography, endorsement by guideline, policies and consensus statements of expanded opioid prescription, implementation of educational interventions and prescription drug monitoring programs, and expanded media coverage.

Because the reasons for increased opioid-related overdose mortality are numerous, diverse, and complex, interventions to reduce opioid-related overdose mortality must vary in their targets. To emphasize its public health importance, in its Fiscal Year 2016 budget, the White House Administration increased funding by $133 million for efforts to combat the prescription opioid epidemic. This funding will support multifaceted efforts to improve education and training, tracking and monitoring, prevention and overdose response, treatment, and enforcement and supply.

Chronic Pain and the Complexity of Chronic Opioid Therapy

Chronic pain may occur in up to 50% of Veterans treated in primary care.[15] Chronic pain is characterized by a persistence of greater than 3 months[16] and its treatment may vary based on patient demographics and comorbidities (*eg*, alcohol or substance use and other mental health and medical disorders).[17] Among individuals with chronic pain, about 25% will develop related life problems, including increasing physical, emotional, and social dysfunction that requires more intensive, multimodal treatment.[18]

Developing evidence-based guidance on how and when to use opioids for chronic non-cancer pain management is difficult because there is little evidence that opioids are effective in maintaining pain relief over long periods of time and inconclusive evidence as to whether opioids can improve long-term functioning and quality of life.[17,19] Clinical policies and practice try to balance the risks of overdose, drug interactions, and complications such as falls and accidental death against the risk of undertreatment of pain.[20] Between 2009 and 2012, many professional society and health care agencies, including the VA/DoD, updated their guidelines to better address opioid risk mitigation, focusing on dosing targets and strategies for identifying signs of misuse.[21] According to Nuckols et al, 9 fair- to good-quality guidelines consistently agree on the following treatment strategies: (1) use of upper dosing thresholds (generally 90-100 mg MED, but some up to 200 mg MED), (2) cautions with certain medications, (3) attention to drug-drug and drug-disease interactions, and (4) use of risk assessment tools, treatment agreements, and urine drug testing for mitigating high-risk use. However, implementation of the

recommended approaches is problematic because the evidence on the effectiveness of such strategies remains weak[21] and questions continue about whether dosing threshold initiatives may be generating a new unanticipated consequence – the emergence of withdrawal symptoms that may lead to aberrant opioid-seeking behaviors that may result in use of illicit opioids.[22,23]

To identify which patients may benefit most from expanded use of non-opioid alternatives, there is a need to first understand who is most at risk for complications related to opioid use. More medical, psychiatric, and substance use disorders and specifically neuropathy, low back pain, nicotine dependence disorders, and guideline-discordant care have been associated with high-dose opioid use both within and outside of the VA.[24,25] In Veterans receiving opioids, receipt of benzodiazepines has been associated with an increased risk of overdose death[26] and mental health disorders, pharmacotherapy, impaired drug metabolism or excretion, pulmonary disorders, specific opioid characteristics, and recent hospital visits have been associated with serious opioid-induced respiratory depression.[27]

Potential Mechanism for CIH in Mitigating High-risk Opioid Use

CIH encompasses a broad range of therapies, including physical modalities (*eg*, acupuncture, massage, chiropractic manipulation), relaxation and mind/body therapies (*eg*, meditation, mindfulness, guided imagery), movement-based therapies (*eg*, yoga, tai chi, other exercise), creative arts therapies, nutritional counseling, self-care, and other naturopathic treatments and herbal medicines.[28] These treatments are used in a variety of pain conditions, including musculoskeletal, arthritis, headache, and fibromyalgia pain, as well as depression, posttraumatic stress disorder (PTSD), and substance use disorders.[29]

Limited evidence suggests that select CIH interventions may be reasonable non-opioid treatment options in general because: (1) CIH is possibly under-utilized in patients prescribed opioids and (2) compared to usual care, magnitude of pain reduction for CIH is potentially comparable to opioids, but without serious side effects. The potential mechanism for CIH interventions in mitigating high-risk opioid use is that if CIH interventions were to effectively treat pain, then physicians could prescribe fewer or lower dose opioids and/or patients could take fewer or lower dose opioids. Although there is already high use of and willingness to try certain CIH modalities among Veterans with chronic non-cancer pain (CNCP) in general,[30] studies show under-use of CIH in patients prescribed opioids.[31,32] Although studies directly comparing CIH and opioids are lacking,[17,33] the most recent and relevant systematic reviews[33-44] show that when CIH interventions are each respectively compared to a common control group of usual care, they have similar magnitudes of pain improvement (SMD range = 0.46 to -3.65). However, it is unclear how applicable CIH's efficacy is to patients taking opioids – particularly at high doses – because CIH studies have often excluded entirely or involved very few and poorly characterized patients prescribed opioids, and there is some evidence that *non-use* of opioids may be a strong predictor of CIH efficacy.[45] For the April SOTA meeting, a small group of CIH and pain researchers will provide a more rigorous synthesis of evidence on the effects of CIH on pain.

We found, however, that opioid-specific guidelines (see Supplemental Materials)[13,46-62] seldom refer directly to CIH treatments. Some guidelines instruct providers to ask themselves, prior to prescribing opioids, "are alternative treatment options available?", but no specific CIH treatments are listed as a possible "alternative" treatment to consider. General chronic pain

guidelines more commonly reference specific CIH interventions – most frequently acupuncture,[54-59] followed by massage,[54,55,58,61] and yoga.[54,55,58] The VHA's current Pain Management Directive (2009-053) also generally mentions CIH as a potential non-pharmacological treatment option, but like other guidelines, does not specify *when* to initiate CIH in relation to opioids. All seem to imply CIH use as generally adjunctive to opioids. National CIH organizations, such as the National Center for Complementary and Integrative Health in the United States and the Complementary Medical Association in United Kingdom, have not yet issued CIH-specific guidelines.

Possible roles for CIH in mitigating high-risk opioid use are: (1) to reduce opioid use in general, by initiating CIH *prior* to initiating opioids, (2) to reduce dose escalation, by integrating adjunctive CIH during the initiation and titration phases and/or as a supplemental therapy for pain exacerbations during stable opioid therapy, and (3) to help manage withdrawal symptoms and potential pain exacerbation during planned opioid dose reduction or complete withdrawal.

Key Considerations in Measuring the Effectiveness of CIH to Reduce Opioid Use

The goal of reducing opioid use is to reduce risk of overdose deaths, dependence, misuse, and other serious complications. In some cases, this means stopping opioids entirely. Because of the link between increased opioid dose and prescription opioid overdose deaths,[8-10] another potentially meaningful indicator of CIH success in reducing opioid use may be to show reductions below relevant and justified MED thresholds. However, given the central goal of risk reduction and the lack of an established magnitude of dose reduction that is agreed upon as clinically important, any mean dose decrease is a reasonable proxy to consider.

Some risks of reducing opioid dose and use may be under-treatment of pain resulting in reduced quality of life and function, the emergence of withdrawal symptoms – potentially related to an opioid use disorder - that may lead to aberrant opioid-seeking behaviors that may result in use of illicit opioids,[23] and perception of withholding care. These potential consequences must be weighed against reductions in opioid use.

There is a need to clarify the applicability of CIH's effects to Veterans who are most representative of patients prescribed high-dose opioids: predominantly male, white, middle-aged, overweight, and with multiple moderate-severe pain problems and high levels of medical and psychiatric comorbidity. Also of interest is determining whether: (1) type or location of pain, (2) patient demographics (*eg*, age, race, ethnicity, gender), and (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities, and high risk for addiction) may modify the effectiveness of CIH for reducing opioid use and whether there is variation by CIH type or timing of use (*eg*, *prior* to initiating opioids; early intervention to prevent "chronification"; or as an adjunct to opioid therapy during initiation, titration, or for exacerbations, or after opioid failure).

SCOPE

The objective of this evidence brief is to summarize the evidence on the effectiveness of select Complementary and Integrative Health (CIH) interventions (acupuncture, massage, meditation, tai chi, and yoga) for reducing opioid use in adults with chronic neck, low back, and large joint pain. The ESP Coordinating Center investigators and representatives of the SOTA committee

worked together to identify the population, interventions, comparators, outcomes, timing, setting, and study design characteristics of interest. The SOTA committee approved the following key questions and eligibility criteria to guide this review:

KEY QUESTIONS

Key Question 1:   In adults with chronic neck, low back, and large joint pain who have never used opioids, what is the comparative effectiveness of selected CIH interventions for reducing new opioid use?

Key Question 2:   In adults with chronic neck, low back, and large joint pain who have never used opioids, what are the comparative harms of selected CIH interventions for reducing new opioid use?

Key Question 3:   In adults with chronic neck, low back, and large joint pain who have never used opioids, how do the comparative effects of selected CIH interventions for reducing new opioid use vary depending on: (1) the specific type or location of pain; (2) patient demographics (*eg*, age, race, ethnicity, gender); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities, and high risk for addiction)?

Key Question 4:   In adults using opioids for chronic neck, low back, and large joint pain, what is the comparative effectiveness of selected CIH interventions for reducing opioid use?

Key Question 5:   In adults using opioids for chronic neck, low back, and large joint pain, what are the comparative harms of selected CIH interventions for reducing opioid use?

Key Question 6:   In adults using opioids for chronic neck, low back, and large joint pain, how do the comparative effects of selected CIH interventions for reducing new opioid use vary depending on: (1) the specific type or location of pain; (2) patient demographics (*eg*, age, race, ethnicity, gender); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities, and high risk for addiction)?

ELIGIBILITY CRITERIA

The ESP included studies that met the following criteria:

· *Population:* Adults with chronic non-cancer neck or low back and large joint pain (*eg*, shoulders, elbows, hips, knees, and ankles)[1]

· *Intervention*: Massage, acupuncture, meditation, yoga, and tai chi

· *Comparator*: No restrictions

· *Outcomes:* Primary = reducing new or ongoing use or dosage of opioids, including physician prescribing or patient consumption; Secondary = pain, functional capacity, quality of life, adverse events

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[1] ACR/EULAR classification from Aletaha et al 2010 in *Arthritis & Rheumatism*.

- _**T**iming:_ No restrictions
- _**S**etting_: No restrictions
- _**S**tudy design:_ No restrictions

METHODS

An evidence brief differs from a full systematic review in that the scope is narrowly defined and some traditional review methods may be streamlined in order to synthesize evidence within a shortened timeframe. An evidence brief does not outline the full context in which the information is to be used and does not present a comprehensive assessment of knowledge on the topic. Brief or rapid review methodology is still developing and there is not yet consensus on what represents best practice.

To identify published articles relevant to the key questions, we primarily relied on reference lists from the large volume of recent and relevant ESP evidence maps and systematic reviews. We started with the 4 evidence maps developed by the ESP on acupuncture, meditation, tai chi, and yoga.[41-44] For massage and to identify newer systematic reviews for the other 4 interventions, our research librarian then searched Ovid MEDLINEÒ, Cochrane Database of Systematic Reviews, PubMed, PsycINFO, and CINAHL from 2014 forward. To identify newer primary studies published subsequent to the prior systematic review searches, our research librarian searched MEDLINE® using terms for the CIH interventions and chronic pain. We determined search start dates for new primary studies based on the end dates of previous systematic reviews: 2009 for acupuncture, 2014 for massage, and 2010 for meditation, tai chi, and yoga. We limited the search to published and indexed articles involving human subjects available in the English language. Additional citations were identified through consultation with content experts. See Supplemental Materials for complete search strategies for both our systematic review and primary study searches.

To identify additional unpublished or ongoing studies or existing programs that have evaluated or will evaluate the effects of specific CIH interventions to reduce opioid use, our research librarian searched the following non-bibliographic database sources: known authors, organization websites, government websites, conference proceedings, academic medical center websites, and Google. We identified known authors by noting authors who repeatedly appeared as authors on relevant publications, as well as through discussion with topic experts. Relevant organizations were identified through mention in recent media publications on the topic, since that captured current programs and research that might not be included in academic literature. We included government agencies that have conducted research on, or provided funding for research on, the opioid crisis. Relevant professional societies that publish conference proceedings were also included, namely the American Pain Society. Also, we searched for programs that connected complementary and alternative treatments to traditional Western medicine programs. Finally, between February 8, 2016 and February 19, 2016, we used Google to identify relevant websites, organizations, programs, and experts in the field. Some keywords used include "opioids epidemic," "opioids crisis," "narcotics," "complementary and alternative medicine," "integrative medicine," "yoga," "acupuncture," "massage," "programs," "centers," and "interventions."

Study selection was based on the eligibility criteria described above. Titles and abstracts were reviewed by one investigator. Full-text articles were reviewed by one investigator and checked by another. All disagreements were resolved by consensus.

We used Cochrane's Risk of Bias Tool to rate the internal validity of controlled trials.[63] We abstracted prespecified data from all included studies and results for each included outcome. All data abstraction and internal validity ratings were first completed by one reviewer and then checked by another. All disagreements were resolved by consensus.

We graded the strength of the evidence based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[64] This approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Strength of evidence is graded for each key outcome measure and ratings range from high to insufficient, reflecting our confidence that the evidence reflects the true effect.

A draft version of this report was reviewed by 6 technical experts as well as clinical leadership. Their comments and our responses are presented in the Supplemental Materials.

The complete description of our full methods can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42016033177).

RESULTS

LITERATURE FLOW

Table 1 displays the number of systematic reviews we reviewed in each intervention area. Overall, most SRs identified did not specifically report analgesic use as an outcome.

Table 1. Identified and Reviewed Systematic Reviews

Source	Total # SRs identified	#SRs reviewed full-text	# SRs evaluating analgesic use	# Primary studies identified
Acupuncture				
ESP map	26	26	4	48
Update search	333	24	0	
Massage				
Search	178	25	0	6
Meditation				
ESP map	9	9	0	1
Update search	65	7	0	
Tai chi				
ESP map	14	14	0	3
Update search	35	11	0	
Yoga				
ESP map	3	3	0	3
Update search	52	6	0	

Figure 1 shows the results of our searches for primary studies. We included a total of 6 studies: 3 on acupuncture, 1 on massage, 1 on meditation, and 1 on yoga. No studies were identified for tai chi.

Figure 1. Literature Flow Chart

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┌─────────────────────────────────┐   ┌─────────────────────────────────┐
│ 631 records identified through  │   │ 61 records identified from       │
│ database searching for primary  │   │ systematic review included       │
│ studies                         │   │ studies                          │
└─────────────────────────────────┘   └─────────────────────────────────┘
                            │                   │
                            ▼                   ▼
          ┌──────────────────────────────────────────────┐
          │ 692 records screened for eligibility after    │
          │ removal of duplicates                          │
          └──────────────────────────────────────────────┘
                            │
                            │          ┌──────────────────────────────┐
                            ├─────────▶│ 514 titles and abstracts      │
                            │          │ excluded                      │
                            │          └──────────────────────────────┘
                            ▼
          ┌──────────────────────────────────────────────┐
          │ 178 full-text articles assessed for           │
          │ eligibility                                    │
          └──────────────────────────────────────────────┘
                            │
  ┌──────────────────────┐  │          ┌──────────────────────────────┐
  │ 6 articles included  │◀─┤          │ 172 full-text articles        │
  │ in synthesis         │  └─────────▶│ excluded                      │
  └──────────────────────┘             │ · 58 with general analgesic   │
                                       │   outcomes but not specific   │
                                       │   opioid outcomes (see        │
                                       │   Supplemental Materials)     │
                                       │ · 114 no analgesic outcomes   │
                                       │   or ineligible population,   │
                                       │   intervention, etcetera      │
                                       └──────────────────────────────┘
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Numerous CIH studies measured analgesic use as a secondary outcome, but the majority did not isolate opioid use and prevalence of opioid use at baseline was generally minimal ($< 10\%$). The exceptions were 6 studies that we included in this review that did isolate opioid use.[1-3,65-67]

Supplemental searching of non-bibliographic database sources (see Supplemental Materials for details, including website links) did not identify any additional unpublished or ongoing studies or existing programs that have evaluated or will evaluate the effects of specific CIH interventions to reduce opioid use. For example, in 2014, NIH's National Center for Complementary and Alternative Medicine, the National Institute on Drug Abuse, and the Veteran Affairs Health Services Research and Development announced that they are providing an estimated $21.7 million over 5 years to 13 projects that explore nondrug approaches to managing pain.[68] Although 4 programs include mindfulness as an intervention, none of those mention evaluation of impact on opioid use. We also identified a protocol for an ongoing large-scale NIH-funded study that will compare the effects of usual care to a primary care-embedded interdisciplinary pain program designed to help patients who are on long-term opioids adopt self-management skills and limit their opioid use (NCT02113592). The protocol specifies morphine equivalents as a planned tertiary outcome measure. Although the intervention includes a yoga-based adapted

movement component, the analysis will not be able to isolate its effects from among those of the other multiple components (*ie*, behavioral health, nurse case management, physical therapy, and pharmacy). Also, although we are aware of many existing programs that offer CIH for pain management, it was unclear how CIH was used in relationship to prescribed opioids within these programs.[69-71] We are also aware of programs that routinely use multidisciplinary approaches to help reduce reliance on pharmacological treatments for pain.[73,74] But we were unable to identify clear descriptions of their approaches to using specific CIH interventions or data on their effectiveness.

We found the published literature to provide little useful information for determining the effectiveness of CIH interventions for reducing opioid use. This is because: (1) very few studies evaluated opioid use in isolation from overall analgesic use, and (2) in those that did, details on key opioid use characteristics (*eg*, timing of initiation, daily opioid dose, and duration of use) were missing altogether[65-67] or nonspecific,[2] or the studies suffered from other methodological limitations.[1,3] Details on key opioid use characteristics were likely limited because, with one exception,[3] studies were not designed to measure opioid use as a key outcome. All studies that evaluated opioid use were randomized controlled trials.

Figure 2 displays the quality indicators of the included studies. Half of the studies were rated high risk of bias[65-67] and half were rated as unclear risk of bias.[1-3] The most common methodological limitations were: (1) lack of blinding of participants, personnel, and outcome assessors, combined with lack of a sham or placebo group, which could have led to more favorable assessments in the intervention groups, and (2) increased risk of attrition bias due to high (47% to 52%) or differential (> 20%) exclusion of outcome data. See the Supplemental Materials for detailed data abstraction, quality assessment, and strength of evidence tables.

Figure 2: Quality Assessment of Included Studies
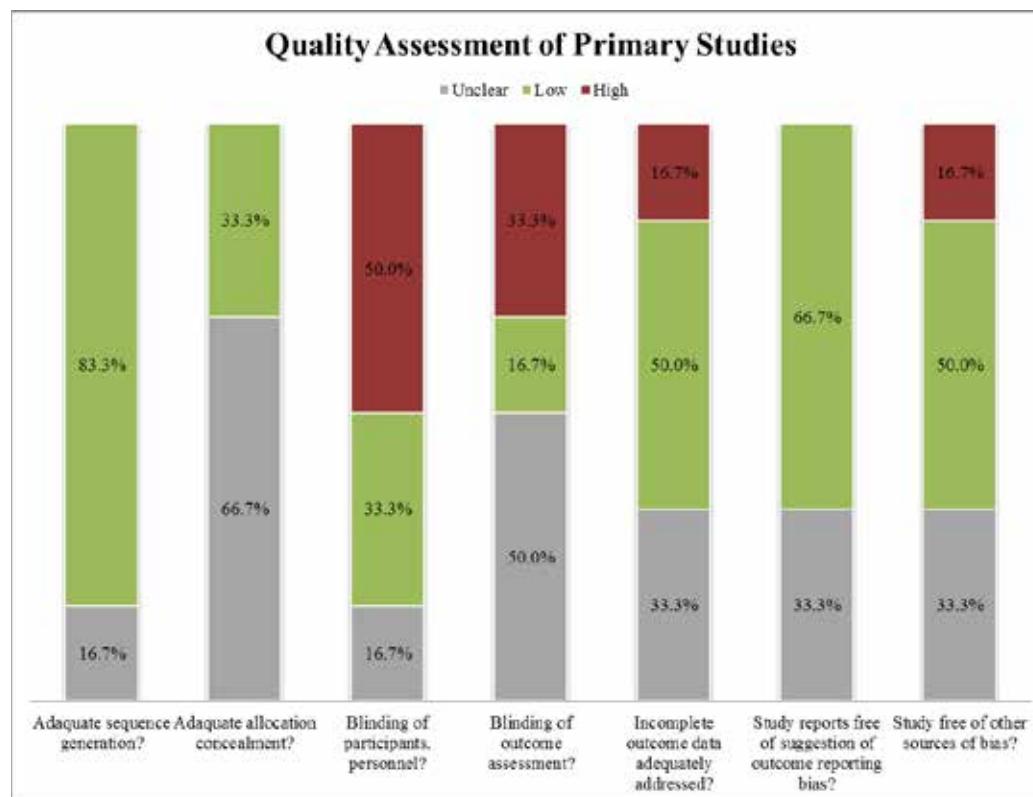
KEY QUESTIONS 1-3: CIH FOR REDUCING NEW OPIOID USE

We found no studies assessing CIH interventions for reducing new opioid use.

KEY QUESTIONS 4-6: CIH FOR MANAGING EXISTING OPIOID USE

Acupuncture

Acupuncture is the only included CIH intervention with any studies that reported at least some information on opioid characteristics.[1-3] Although actual mean baseline MED were only reported in one study (42.2-65.9 mg/d),[3] based on very low numbers of daily mean doses (0.07-0.12) in the other 2 studies, we can assume that opioid dose was very low in these studies.[1,2] Compared to sham, there is low-strength evidence that certain acupuncture modalities have shown some modest promise for reducing opioid dose during the 8-10 week treatment periods, both in Veterans with advanced knee osteoarthritis using a mean of 0.47 weekly doses of unspecified opioids,[2] and in patients with various forms of chronic pain from an Australian chronic pain center undergoing planned opioid tapering (Table 2).[3] However, these effects were not sustained 5-9 months following acupuncture discontinuation.

In 190 Veterans with advanced knee osteoarthritis, compared to sham, stimulation of the periosteum (PST) facilitated by acupuncture needles once a week for 10 weeks led to a small reduction in the number of weekly opioid doses (mean difference, -0.27; 95% CI -0.48 to -0.054) immediately after treatment period.[2] But these results weren't sustained at 9 months (mean difference, -0.20; 95% CI -0.23 to 0.19). Adding boosters every 2 weeks and then monthly

following the initial 10-week treatment period did not further reduce weekly opioid doses compared to sham. Strengths of this study include: (1) this is the only study in a VA population, and (2) intended patient blinding was formally assessed and documented as successful. For other outcomes measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), PST without boosters did not improve pain, function, or quality of life at 10 weeks or 9 months. PST with boosters led to a statistically significant lower mean WOMAC pain score at 9 months (6.2 vs 7.7; mean difference, 1.5; 95% CI 0.069 to 3.0); however, the clinical importance of a 1.5-point difference is unclear. A 20-30% improvement has been suggested as a threshold for minimum clinically important difference in pain[19] and both the PST booster group (8.9 at baseline to 6.2 at 9 months; 30% reduction) and the control group (10.6 at baseline to 7.7 at 9 months; 27% reduction) are in that range. PST with boosters did not improve quality of life or function. An advantage of this study is that it is highly applicable to patients prescribed opioids in the VA as it involved a VA population that was mostly male (85%), had a mean age of 67 years, had been suffering moderate pain for a mean of 6 years, and had a mean Comorbidity Cumulative Illness Rating of 4.4 (number of items with a score of moderate or higher).

In 35 patients with various forms of chronic pain from an Australian chronic pain center undergoing planned opioid tapering, compared to sham, electroacupuncture for 20 minutes twice a week for 6 weeks did not lead to a statistically significant reduction in opioid MED either at the end of treatment or at 20 weeks.[3] Strengths of this study include: (1) this is the only study designed to measure opioid use as a primary outcome, (2) this is the only study we found that reported opioid type (*ie*, codeine, methadone, oxycodone, morphine, and tramadol) and MED, but MED was greater in the real acupuncture group than in the sham group (461.6 mg MED/wk or 65.9mg/d versus 295.5mg MED/w or 42.2mg/d), (3) patients recorded medication use daily, rather than retrospectively for the previous week, and (4) intended patient blinding was formally assessed and documented as successful. In the intention-to-treat population, the reduction in opioid MED was 39% in the real acupuncture group and 26% in the sham group, which likely did not reach statistical significance because of the small sample size. However, the difference may have been biased in favor of the real acupuncture group because of the greater starting MED (65.9 mg MED/d vs 42.2 mg MED/d). Real electroacupuncture did not significantly improve pain, depression, or quality of life, and functional capacity was not evaluated. The applicability of this study to patients prescribed opioids in the VA is unclear. Patients were 50% male and in their early 50s, with a mean pain duration of 15 years. Mean pain intensity was 5 based on a patient diary visual analogue scale (VAS), but the VAS scale upper limit was not reported. Comorbidities were not reported.

In the third trial with at least some detail on opioid dosing, in 61 low back pain patients seen at an Austrian university-based pain center, auricular acupuncture with electrical stimulation reduced total mean number of tramadol 50 mg rescue medication tablets consumed over an 18-week period compared to acupuncture without electrical stimulation (6 versus 150; P < .001).[1] Acupuncture was performed once weekly for 6 weeks. A strength of this study is that patients recorded medication use 3 times daily, rather than just once daily or retrospectively for the previous week. However, the lack of a sham or placebo group is an important limitation of this study, which limits our ability to attribute the opioid reductions to the acupuncture itself, rather than other nonspecific features of study participation. Other benefits of electroacupuncture included reduced pain at 18 weeks (VAS estimated from Figure 2A: 1 versus 4; P < .05), more patients returning to full-time work (77% vs 25%; P = .0032), and reduced impairment in well-

being (VAS estimated from figure 2B: 1 vs 5; P < .05). The applicability of these findings to patients prescribed opioids in the VA is also unclear as patients were 30% male and comorbidities were not reported.

Massage

There is insufficient evidence to draw conclusions about the effects of massage on opioid use. In 401 Group Health Cooperative members with chronic low back pain, compared to usual care, structural or relaxation massage did not reduce the proportion of patients who reported any narcotic analgesic use in the preceding week immediately following 10 weeks of treatment, or after 26 or 52 weeks of follow-up (Table 2).[65] The meaningfulness of this finding is unclear, however, as details are lacking about opioid type, dose, and frequency. The other key limitation of this study is that it has a high risk of performance and detection biases that could have led to more favorable assessments in the massage groups. This is because opioid use was retrospectively assessed for the previous week based only on unmasked patient self-report and there was not a sham treatment group.

Meditation

There is insufficient evidence to draw conclusions about the effects of meditation on opioid consumption. Compared to waitlisted usual care, in 25 patients with failed back surgery syndrome (FBSS) an 8-week mindfulness stress reduction (MBSR) program, including weekly classroom learning and audiotape-guided meditation for 45 minutes per day for 6 days a week, led to reduced overall analgesics medication use (Table 2).[66] However, this finding has little usefulness for determining impact specifically on opioid use, due to limitations in the measurement method. The 4-point medication use scale included ratings specific to both non-opioid and opioid use (0 = no analgesic use, 1 = less than daily non-opioid analgesic use, 2 = daily non-opioid analgesic use, *3 = less than daily opioid use, and 4 = daily opioid use*). However, we can't determine whether the point reductions (0.4-1.5) observed related to opioid use because baseline levels were not reported. For example, the 1.5-point reduction in the MBSR group could have reflected a change from daily non-opioid use to no analgesic use. A better way to capture opioid use would have been to evaluate proportion of patients who scored a 3 or 4, as both ratings specifically reflecting opioid use. Even then, without details of opioid type and dose, we can't assess whether the reductions are truly meaningful. Interpretation of these findings is also limited by their general high risk of performance and detection biases caused by reliance on self-rated outcomes from unblinded patients and the lack of a sham treatment.

Yoga

There is insufficient evidence to draw conclusions about the effects of yoga on opioid consumption. In 95 predominantly low-income female minorities with moderate-severe chronic low back pain from an academic safety-net hospital and 5 affiliated federally qualified community health centers in Boston, changes from baseline in proportion of patients using opioids after 12 weeks of once-weekly or twice-weekly yoga were small and not different between groups (Table 2).[67] Interpretation of these findings is limited by: (1) the lack of information about opioid type and dose, (2) their general high risk of performance and detection biases caused by reliance on self-rated outcomes from unblinded patients, (3) the lack of a sham treatment group, (4) low and differential adherence to the yoga treatment (once-weekly = 65% vs twice-weekly = 44%, P = .040), (5) potential contamination of effects by use of other CIH (*eg,*

47% used massage), and (6) unknown influence of paying subjects $25 every 3 weeks for their participation.

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Evidence-based Synthesis Program

Table 2: Summary of Findings

Author Year Risk of Bias N Pain type	Interventions	Applicability (% male, age, comorbidities, pain severity and duration)	Opioid type and dose	Impact on opioid use	Pain, quality of life, functional status, adverse events
Acupuncture					
Sator-Katzenschlager 2004 [1] Unclear N = 61 LBP	Auricular acupuncture with electrical stimulation (EA) or without stimulation (CO)	Unclear: 30% male, age=53.6; moderate pain for 4.6y; comorbidities NR	Tramadol: ≤ 400 mg daily	ê Opioid consumption (# tablets) throughout intervention: EA = 6 vs CO = 150 (P < .001)	ê Pain (VAS scale out of 10) at18 wks: EA = 1 vs CO = 4 (P < .05) ê Well-being impairment (scale out of 10) at 18 wks: EA = 1 vs CO = 5 (P < .05) Adverse events: none observed
Weiner 2013 [2] Unclear N = 190 Knee OA	Periosteal stimulation therapy, with boosters (PST+PST) or without boosters (PST+control) or control PST without boosters (control)	High: VA population, 85% male in mid to late 60s with comorbidities	Opioid type NR: average 0.47 doses/wk	Opioid consumption (baseline adjusted differences in # weekly doses compared to control) at 10 wks: = PST+PST: 0.018 (95% CI -0.19 to 0.23) ê PST+control: -0.27 (95% CI -0.48 to -0.054)	Baseline adjusted differences compared with control at 9 m PST+PST improved WOMAC pain (MD 1.5, 95% CI 0.069 to 3.0), but not SF-36 physical component (MD -1.2; 95% CI -2.8 to 0.041) vs Control PST PST+control did not improve WOMAC pain (MD 1.1, 95% CI -.32 to 2.6) or SF-36 physical component (MD -1.3; 95% CI -3.0 to 0.28) vs Control PST Adverse events: 4 adverse events attributable to PST and control PST
Zheng 2008 [3] Unclear N = 35 NMP	Electroacupuncture (REA) or sham electroacupuncture (SEA)	Unclear: 50% male in early 50s, 15 years duration; pain intensity unclear – measured on VAS scale, average = 5, but not clear on VAS upper limit; Comorbidities NR	Codeine, Methadone, Oxycodone, Morphine, & Tramadol Dose (mg/d morphine equivalent): REA = 65.9/d	ê OLM consumption (change from baseline, mg/d morphine equivalent) at 8 wks: REA = -25.7 vs -10.9 SEA and 20 wks: REA = -16.7 vs SEA = -8.1	ê Pain (scale NR): Change from baseline at 8 wks: -0.8 REA vs -0.7 SEA (P = .001) Adverse events: 33 events REA and 19 events SEA

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			SEA = 42.2/d		
Massage					
Cherkin 2011 [65] High N = 401 LBP	Structural massage (SM), relaxation massage (RM), or usual care (UC)	Unclear: 35.67% male, age=47; moderate pain (5.67/10 on symptom bothersome scale), 75.6% LBP longer than 1 year; co-morbidities NR	NR	= narcotic analgesic consumption (% narcotic analgesics in past week, change from baseline) at 10 wks: SM = -12.4 vs RM = -12.0 vs UC = -7.2 at 52 wks: SM = -12.2 vs RM = -12.1 vs UC = -8.1	= Pain (change from baseline symptom bothersomeness score out of 10): at 10 wks: -1.8 SM vs -2.1 RM vs -0.6 UC at 52 wks: -1 SM vs -1.7 RM vs -1.6 UC é Quality of life (% patient global rating of improvement): at 10 wks: SM = 36.1 (28.8 to 45.) vs RM = 39.4 (31.8 to 48.7) vs UC = 3.8 (1.6 to 9.0) UC (P = <.001) at 52 wks: SM = 26.1 (19.8 to 34.6) vs RM = 36.2 (29.1 to 45.0) vs UC = 20.5 (14.5 to 29.0) UC (P = .013) Adverse events: 7% SM and 4% RM patients
Mindfulness					
Esmer 2010 [66] High N = 25 FBSS	Mindfulness-based stress reduction (MBSR) or usual care	Unclear: 56% male, age=55.08; moderate-severe pain (23.64/30 on VAS pain scale), duration less than 2 years; co-morbidities NR	NR	ê Analgesic medication use at 12-wks (4-point scale: 0 = no analgesic to 4 = daily narcotics): MBSR = -1.5 vs Control = 0.4 (P < .001)	ê Pain (change in VAS 30-point scale) at 12 wks: MBSR = -6.9 vs control = -0.2 (P < .021) é Quality of life: Change in CPAQ (108-point scale) at 12 wks: MBSR = 7.0 vs control = -6.7 (P < .014) é Functional status (change in RMDQ 24-point scale) at 12 wks: MSBR=-3.6 vs control = 0.1 (P < .005)
Yoga					
Saper 2013 [67] High N = 95 LBP	Yoga, once weekly classes or twice weekly classes	Unclear: 28% male, age=47.5; moderate pain (6.9/11 in previous week), duration=43% longer	NR	= Opiate (% change from baseline) at 12 wks: Yoga 1x/wk = 0 vs Yoga 2x/wk = 2; NS	=Pain (change from baseline out of 11) at 12 wks: 1x/wk classes -2.1 (95% CI -2.9 to -1.3) vs 2x/wk classes -2.4 (95% CI -3.1 to -1.8); Between group difference: 0.3 (95% CI -0.2 to 0.8)

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		than 1 year; co-morbidities NR			= Quality of life (SF-36 mental mean change from baseline) at 12 wks: 1x/wk classes 4.0 (1.3 to 6.7) vs 2x/wk classes 2.5 (-0.7 to 5.7); Between group difference: 1.5 (-2.6 to 5.6)
					=Adverse events: 27% 1x/wk classes, 34% 2x/wk classes (P = 0.47)

EA: Auricular acupuncture with stimulation; CO: Auricular acupuncture without stimulation; LBP: Low back pain; OA: Osteoarthritis; PST: Periosteal stimulation therapy; NR: Not reported; NMP: Non-malignant pain; REA: Electroacupuncture; SEA: Sham electroacupuncture; OLM: Opioid-like medication; VAS: Visual Analog Scale; WOMAC: Western Ontario & McMaster Universities Osteoarthritis Index; CPAQ: Chronic Pain Acceptance Questionnaire; RMRQ: Roland Morris Disability Questionnaire; SF-36: Short Form-36 Health Survey; SM: Structural massage; RM: Relaxation massage; UC: Usual care; MSBR: Mindfulness-based stress reduction; FBSS: Failed back surgery syndrome

KEY MESSAGES

1. The evidence base regarding the effectiveness of select CIH interventions for reducing opioid use in patients with chronic pain is extremely limited. No study has evaluated the effectiveness of select CIH interventions for reducing new opioid use, stopping opioids entirely, or for reducing opioid use below any particular morphine equivalent dose (MED) threshold.

2. Compared to sham, in patients already using dosage below 80 mg MED, there is low-strength evidence that certain electro-acupuncture modalities can reduce opioid dose immediately after 6- to 10-week treatment periods, both in a group of Australian patients with various forms of chronic pain undergoing a planned opioid tapering and in a group of Veterans with advanced knee osteoarthritis who were taking opioids for an unknown duration. But these effects were not sustained 5-9 months following acupuncture discontinuation.

3. Single studies of massage, meditation, and yoga provided insufficient evidence to draw conclusions about their effects on opioid dose because: (1) they lacked details about opioid type, dose, and frequency, and (2) relied on self-assessments from unblinded patients, with no effort to match the intervention to a sham treatment group, which could have led to more favorable assessments in the experimental groups.

4. We found no studies of the effects of classic acupuncture or tai chi on opioid use.

5. We found no studies that evaluated whether the effectiveness of CIH varies depending on: (1) type or location of pain, (2) patient demographics (*eg*, age, race, ethnicity, gender), or (3) patient comorbidities (including past or current nicotine, alcohol, or substance use disorders, mental health disorders, medical comorbidities, and high risk for addiction).

6. We did not identify any existing or developing programs primarily designed to offer CIH interventions *before* opioids or to reduce opioid use. Several programs exist to promote use of interdisciplinary approaches, including CIH interventions, but are not designed to isolate the effects of the CIH interventions and measure changes in opioid use as secondary outcome.

IMPLICATIONS FOR FUTURE RESEARCH

Additional research is needed to better understand the effectiveness of select CIH interventions for reducing opioid use in Veterans. Patient self-report methods for measuring opioid use varied substantially across studies, generally without providing a rationale for how they were selected: recall periods ranging from multiple times daily up to monthly, proportion of patients with any use, daily, or less than daily use, and number of weekly doses. To determine how to select and strengthen patient self-report methods for measuring opioid use, we suggest considering use of well-validated processes, optimized question response formats and recall periods, taking steps to address social desirability concerns, avoiding interview-based assessments, and accounting for self-report challenges such as cognitive functioning, burden, and setting.[75] Potentially, incorporation of the patient perspective and preference in selecting measurement methods may

further improve patient satisfaction and the reliability of their self-report. To improve clinical relevance, future studies should report opioid type, dose, and frequency. In addition to opioid use outcomes, to best assess the overall net benefit of CIH interventions, future studies should simultaneously evaluate a more complete set of key outcomes, including their impact on pain, pain-related function, quality of life, and harms.

A dataset such as Morasco et al used to study clinical characteristics of Veterans prescribed high doses of opioid medications (Veterans Integrated Service Network-20 Data Warehouse)[24] potentially could be further evaluated to assess the effects of CIH use on opioid dose. Although the Morasco study focused on patient demographics and clinical characteristics, variables could be added to represent CIH use to evaluate their potential association with progression of opioids from traditional to high doses. However, as a concern with reducing opioid dose and use is the possible increase in risk of under-treatment of pain and other undesirable outcomes such as reduced quality of life, function, and switch to other opioids (such as heroin), we recommend additional studies that simultaneously measure these potential consequences.

To improve our knowledge about the state of CIH practice in relation to opioids, research is needed to identify whether the effectiveness of CIH varies depending on the timing of their integration. To facilitate this, future studies should seek to more clearly characterize when their populations initiated CIH in relation to opioids using the framework for opioid treatment management from the VA/DoD guideline: (1) early intervention *prior* to initiating opioids, to prevent "chronification," (2) as an adjunct during initiation, titration, for exacerbations, or after opioid failure, or (3) to facilitate opioid withdrawal.

Future research should also seek to clarify whether there are particular subpopulations that are more or less likely to benefit from CIH to reduce opioid use and whether variation in benefit varies by CIH type. Key characteristics of interest include: (1) type or location of pain, (2) patient demographics (*eg*, age, race, ethnicity, gender), and (3) patient comorbidities (including past or current nicotine, alcohol, or substance use disorders, mental health disorders, medical comorbidities, and high risk for addiction). We also suggest investigation of how patient motivation, mobility, and geography may impact benefit from CIH to reduce opioid use. This is because these factors may impact Veterans' abilities to successfully access skilled practitioners of CIH treatments.

Research into potential barriers to CIH implementation may also be useful. Several CIH therapies require a higher level of provider time and patient effort than treatment with opioids. Access to skilled practitioners of CIH treatments may vary depending on patient motivation, mobility, geography, and cost. CIH treatments vary in their required levels of active patient and provider engagement and this variation may ultimately impact feasibility, adherence, and effectiveness. The "passive" nature of acupuncture and massage may seem more approachable to patients. But they both require direction by and presence of a provider and potentially more frequent clinic visits and higher cost. These features may be more difficult to navigate for Veterans in rural areas with transportation limitations. However, both treatments could potentially be provided in patients' homes. Yoga and tai chi have the potential advantage of being the least provider-intensive, as both can be delivered in Veterans' home via various modalities (*eg*, internet streaming, videotape, *etc*). But yoga and tai chi also require the greatest

amount of patient motivation and physical activity and may be at least initially the most difficult for patients with lower mobility and greater pain.

ACKNOWLEDGEMENTS

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