

Mind-Body Therapies for Opioid-Treated Pain

A Systematic Review and Meta-analysis

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IMPORTANCE Mind-body therapies (MBTs) are emerging as potential tools for addressing the opioid crisis. Knowing whether mind-body therapies may benefit patients treated with opioids for acute, procedural, and chronic pain conditions may be useful for prescribers, payers, policy makers, and patients.

OBJECTIVE To evaluate the association of MBTs with pain and opioid dose reduction in a diverse adult population with clinical pain.

DATA SOURCES For this systematic review and meta-analysis, the MEDLINE, Embase, Emcare, CINAHL, PsycINFO, and Cochrane Library databases were searched for English-language randomized clinical trials and systematic reviews from date of inception to March 2018. Search logic included (pain OR analgesia OR opioids) AND mind-body therapies. The gray literature, ClinicalTrials.gov, and relevant bibliographies were also searched.

STUDY SELECTION Randomized clinical trials that evaluated the use of MBTs for symptom management in adults also prescribed opioids for clinical pain.

DATA EXTRACTION AND SYNTHESIS Independent reviewers screened citations, extracted data, and assessed risk of bias. Meta-analyses were conducted using standardized mean differences in pain and opioid dose to obtain aggregate estimates of effect size with 95% CIs.

MAIN OUTCOMES AND MEASURES The primary outcome was pain intensity. The secondary outcomes were opioid dose, opioid misuse, opioid craving, disability, or function.

RESULTS Of 4212 citations reviewed, 60 reports with 6404 participants were included in the meta-analysis. Overall, MBTs were associated with pain reduction (Cohen $d = -0.51$; 95% CI, -0.76 to -0.26) and reduced opioid dose (Cohen $d = -0.26$; 95% CI, -0.44 to -0.08). Studies tested meditation ($n = 5$), hypnosis ($n = 25$), relaxation ($n = 14$), guided imagery ($n = 7$), therapeutic suggestion ($n = 6$), and cognitive behavioral therapy ($n = 7$) interventions. Moderate to large effect size improvements in pain outcomes were found for meditation (Cohen $d = -0.70$), hypnosis (Cohen $d = -0.54$), suggestion (Cohen $d = -0.68$), and cognitive behavioral therapy (Cohen $d = -0.43$) but not for other MBTs. Although most meditation ($n = 4$ [80%]), cognitive-behavioral therapy ($n = 4$ [57%]), and hypnosis ($n = 12$ [63%]) studies found improved opioid-related outcomes, fewer studies of suggestion, guided imagery, and relaxation reported such improvements. Most MBT studies used active or placebo controls and were judged to be at low risk of bias.

CONCLUSIONS AND RELEVANCE The findings suggest that MBTs are associated with moderate improvements in pain and small reductions in opioid dose and may be associated with therapeutic benefits for opioid-related problems, such as opioid craving and misuse. Future studies should carefully quantify opioid dosing variables to determine the association of mind-body therapies with opioid-related outcomes.

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JAMA Intern Med. doi:10.1001/jamainternmed.2019.4917
Published online November 4, 2019.

The opioid crisis is being addressed with heightened urgency at both clinical and policy levels. For much of the 20th century, opioids were prescribed primarily for postoperative and cancer-related pain.¹ In the 1990s, prescription of opioids to treat all forms of pain became standard care.¹ Consequently, opioid prescriptions increased to 208 million by 2011.¹ Currently, more than 35% of the US adult population is prescribed opioids in a given year.² This marked increase in opioid prescriptions was paralleled by an increasing incidence of opioid use disorder (OUD), which now affects approximately 2 million individuals in the United States,³ and opioid misuse, which affects 12 million individuals in the United States overall.² Since 2006, US deaths due to opioid overdose have tripled, increasing to 42 200 in 2016,⁴ and are projected to reach 82 000 by 2025, resulting in 700 000 additional deaths in the United States.⁵

The opioid crisis arose in part because of well-intentioned efforts to alleviate untreated pain. Although opioids are considered to be useful in managing a wide continuum of pain, including acute, procedural, and chronic pain, evidence of their long-term efficacy and safety is limited.⁶ To help combat the opioid crisis, guidelines encourage practitioners to consider nonopioid pain management options, including mind-body therapies (MBTs).⁷ Mind-body therapies target “interactions among the brain, mind, body, and behavior, with the intent to use the mind to affect physical functioning and promote health.”⁸ Mind-body therapies might ameliorate pain and prevent downstream transitions from long-term opioid use to OUD. Thus, the National Institutes of Health initiative Helping to End Addiction in the Long Term (HEAL) has called for studies of MBTs as interventions for pain and OUD.

The efficacy of MBTs should be examined across the pain continuum. Reviews⁹⁻¹⁴ demonstrate that MBTs may be associated with significantly alleviated clinical pain. Few of the studies reviewed measured opioid use, and reviews included patients who were not prescribed opioids. However, no review, to date, has examined the efficacy of MBTs specifically for the subset of patients prescribed opioid analgesics. Given the importance of this population, we provide, to our knowledge, the first systematic review of MBTs for opioid-treated pain. Because of the urgency of the opioid crisis, we reviewed all studies of MBTs for patients with opioid-treated pain regardless of the study quality or clinical population to provide comprehensive evidence to prescribers, patients, payers, and policy makers.⁷

Methods

Literature Search

For this systematic review and meta-analysis, the following bibliographic databases were searched for English-language randomized clinical trials and systematic reviews from the date of inception to March 2018: MEDLINE, Embase, CINAHL, Emcare, PsychINFO, and Cochrane Library. Search logic included (pain OR analgesia OR opioids) AND mind body therapies (eMethods in the Supplement). We searched gray literature

Key Points

Question Are mind-body therapies (ie, meditation, hypnosis, relaxation, guided imagery, therapeutic suggestion, and cognitive behavioral therapy) associated with pain reduction and opioid-related outcome improvement among adults using opioids for pain?

Findings In this systematic review and meta-analysis of 60 randomized clinical trials with 6404 participants, mind-body therapies were associated with improved pain (Cohen $d = -0.51$; 95% CI, -0.76 to -0.27) and reduced opioid dose (Cohen $d = -0.26$; 95% CI, -0.44 to -0.08).

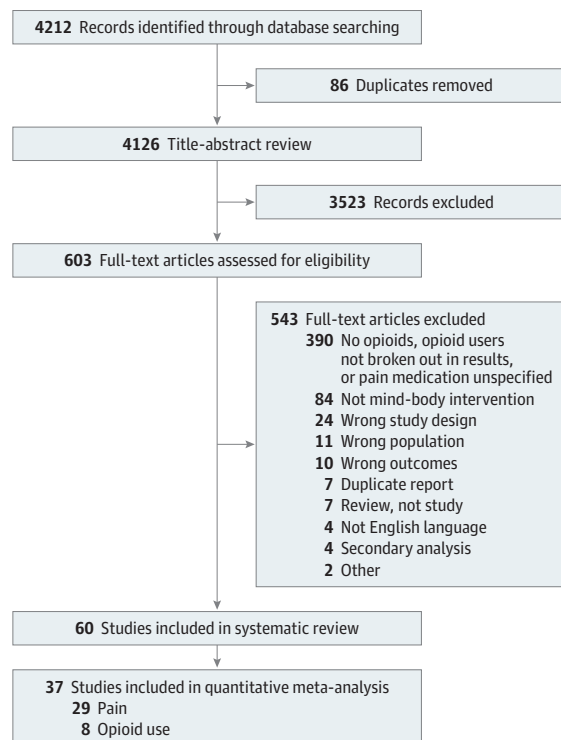
Meaning Practitioners should be aware that mind-body therapies may be associated with moderate improvements in pain and small reductions in opioid dose.

and ClinicalTrials.gov and performed hand searches of relevant bibliographies. The methods and reporting of this systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Figure 1).¹⁵

Inclusion and Exclusion Criteria

Randomized clinical trials of MBTs were included if they involved adults (aged ≥ 18 years) prescribed opioids for chronic, acute, procedural, or cancer pain. Because we were focused

Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis Flow Diagram of Literature Search and Study Inclusion



on both pain and opioid use outcomes, studies that did not include pain-related outcomes were excluded (eg, studies of individuals with OUD who did not report pain). Studies were excluded if they collected data on pain medicine or analgesics without specifying that these medications were opioids.

To constrain the considerable heterogeneity of MBTs, we limited our review to studies of psychologically oriented MBTs that prioritize using mental techniques to ameliorate pain, including meditation, hypnosis, guided imagery, relaxation, therapeutic suggestion, and cognitive behavioral therapy (CBT). Meditation involves practices, such as mindfulness, to cultivate present-moment focused attention and meta-awareness, as well as acceptance of thoughts, emotions, and body sensations.¹⁶ Hypnosis involves induction of an altered state of consciousness in which focused attention and reduced peripheral awareness enhance the capacity for responding to suggestions for changing thoughts, emotions, and sensations.¹⁷ Guided imagery involves active imagination of visual, auditory, and somatic sensations and perceptions.¹⁸ Relaxation involves the use of the mind to systematically release muscle tension throughout the body.¹⁹ Therapeutic suggestion involves provision of suggestions to change thoughts, emotions, and sensations without directly inducing a hypnotic altered state.²⁰ Cognitive behavioral therapy involves the use of logic to challenge and change negative thinking patterns, thereby decreasing negative emotions and promoting adaptive behaviors.²¹

Although acupuncture and spinal manipulation are sometimes labeled MBTs, given that these approaches rely on physical (eg, needling and musculoskeletal adjustment) rather than psychological techniques, we did not include studies of these therapies in our review. Similarly, studies of yoga or Tai Chi without formal meditation practice were excluded. We included studies of physical mind-body modalities or other complementary therapies only if 50% or more of the intervention involved delivery of psychologically oriented MBT techniques. We elected to focus our review on MBTs that primarily use mental techniques because they may be more accessible to people whose mobility is compromised by pain or used for pain relief during inpatient procedures when patients are immobilized.

Types of Outcome Measures

The primary outcome was pain severity or intensity. Secondary outcomes were opioid use measured by prescription record, self-report, or urine toxicologic screening; opioid misuse and craving; and disability or functional impairment.

Data Extraction and Analysis

Abstracts and full texts were screened and data extracted independently by 2 reviewers (E.L.G., C.E.B., A.W.H., E.J.R., R.M.A., S.A.G., K.R.F., J.Y., and/or M.F.) via Covidence (<https://www.covidence.org/home>). Risk of bias was assessed in Covidence using the Cochrane risk of bias tool by 2 independent reviewers (E.L.G., C.E.B., A.W.H., E.J.R., R.M.A., S.A.G., K.R.F., J.Y., and/or M.F.). Disagreements were resolved by a third reviewer (E.L.G., C.E.B., A.W.H., E.J.R., R.M.A., S.A.G., K.R.F., J.Y., or M.F.) or by discussion. To prevent conflict of interest,

studies written by review authors were assessed by other members of the author team.

Mixed-effects meta-analyses were performed using the R Metafor package²² for pain and opioid dose outcomes. After sending email requests for missing data to authors of studies included in the review who did not provide sufficient data in the original publication, 29 studies^{19,23-50} were included in the pain meta-analysis and 8 studies^{29,30,35,37-39,42,43} in the opioid dose meta-analysis. In studies with more than 1 MBT arm, data from both MBTs were included. Studies that reported *P* values but did not report numerical means and SDs for baseline or postintervention pain or opioid use could not be included in the meta-analysis. Pain values were standardized using a 0- to 10-point numeric rating scale, and opioid dose was standardized into morphine equivalents using standard equianalgesic conversion tables.⁷ Change scores were created by subtracting the baseline value from the most proximal postintervention end point; this end point was selected because it was consistently collected despite great variability in time points across studies. The SDs of the change scores were imputed via Cochrane best practices.⁵¹ Effect size estimates were calculated as standardized mean differences.²² Study heterogeneity was investigated using Baujat plots in conjunction with the *Q* and *I*² statistics.^{52,53} Publication bias was examined with funnel plots and the Egger test.^{53,54} Although we performed quantitative meta-analyses on all studies for which we could extract data, the entire body of studies was systematically reviewed in a qualitative manner (summary study data^{19,23-50,55-86} are presented in **Table 1** and detailed study data in the eMethods in the **Supplement**).

Results

Overview of Studies

We screened 4212 citations and 603 full-text articles. Sixty studies with a total of 6404 participants were ultimately included in the review (Figure 1). The 60 studies focused on various clinical pain targets: procedural pain (*n* = 39), burn pain (*n* = 7), cancer pain (*n* = 5), chronic pain (*n* = 8), or heterogeneous acute pain conditions (*n* = 1). Sample sizes ranged from 13 to 500. Studies tested meditation (*n* = 5), hypnosis (*n* = 25), relaxation (*n* = 14), guided imagery (*n* = 7), therapeutic suggestion (*n* = 6), and CBT (*n* = 7) interventions. Studies used a range of control conditions, including another MBT (*n* = 4), psychotherapy comparators (*n* = 11), attention control (*n* = 10), information control (*n* = 7), music controls (*n* = 6), waiting list control (*n* = 2), usual care (*n* = 20), or other control conditions (*n* = 3) (eTables 1-6 in the **Supplement**).

Mindfulness or Meditation Studies

Association of Meditation With Pain Outcomes

All 5 mindfulness or meditation studies^{25-27,55,57} (100%) reported significant improvements in pain severity, pain unpleasantness, interference, thermal pain sensitivity, and/or cessation of postsurgical pain. Meta-analytic results indicated that meditation had a significant strong association with pain reduction (Cohen *d* = -0.70; 95% CI, -1.09 to -0.31; *P* < .001)

Table 1. Mind-Body Therapy Study Descriptions

Source	Clinical Target	No. of Patients	Mind-Body Therapy	Comparator(s)	Session Extensiveness, Format	Pain-Related and Opioid Outcomes (Length of Follow-up)
Meditation Studies						
Dindo et al, ⁵⁵ 2018	Orthopedic surgery	76	Acceptance and Commitment Therapy	Usual care	Single, in person	Cessation of pain (3 mo ^a) Cessation of opioids (3 mo ^a)
Esmer et al, ²⁷ 2010	Failed back surgery	44	Mindfulness-Based Stress Reduction	Waiting list	Multiple, in person	Pain intensity (12 wk, ^a 40 wk ^a) Opioid use (12 wk, ^a 40 wk ^a)
Garland et al, ^{25,56} 2014 and Garland et al, ²⁶ 2017	Chronic pain and taking opioids most days for 90 d	115	Mindfulness-Oriented Recovery Enhancement	Support group	Multiple, in person	Pain severity (8 wk, ^a 3 mo ^a) Pain interference (8 wk, ^a 3 mo ^a) Desire for opioids (8 wk, ^a 3 mo ^{a,b}) Cue-elicited craving (8wk ^a) Opioid use disorder (8 wk, ^a 3 mo ^b) Pain intensity (EMA) (during treatment ^a)
Garland et al, ²⁶ 2017	Hospital inpatients reporting intolerable pain or inadequate pain control	244	(1) Mindfulness training, (2) hypnotic suggestion	Pain education	Single, in person	Pain intensity (after treatment ^b) Pain unpleasantness (after treatment ^a) Desire for opioids (after treatment ^b)
Zgierska et al, ⁵⁷ 2016	Back pain	35	Meditation-based CBT	Usual care	Multiple, in person	Pain severity (8 wk, ^a 26 wk ^a) Opioid dose (8 wk, ^b 26 wk ^b) Pain sensitivity to thermal stimuli (8 wk, ^a 26 wk ^c)
Hypnosis Studies						
Ashton et al, ⁵⁸ 1997	Cardiac surgery	32	Self-hypnosis	Usual care	Single, in person	Opioid dose (hypnosis-compliant patients only, postoperative ^a) Intraoperative medication (postoperative ^b)
Akgul et al, ⁴⁶ 2016	Cardiac surgery	44	Hypnosis	Usual care	Single, in person	Pain intensity (postoperative ^b) Opioid dose (postoperative ^a)
Askay et al, ³¹ 2007	Burn pain	46	Hypnosis	Attention control	Single, in person	Pain intensity (MPQ) (after wound dressing ^b) Pain intensity (GRS) (after wound dressing ^b)
Enqvist et al, ⁵⁹ 1997	Dental surgery	69	Hypnosis	Usual care	Single, recording	Pain intensity (postoperative ^b) Opioid dose (postoperative ^a)
Everett et al, ³² 1993	Burn pain	32	(1) Hypnosis plus placebo, (2) hypnosis plus lorazepam	(1) Psychological intervention plus placebo, (2) psychological intervention plus lorazepam	Single, in person	Pain intensity (after wound dressing ^b) Opioid dose (after wound dressing ^b)
Faymonville et al, ⁴⁷ 1997	Elective plastic surgery	60	Hypnosis	Stress-reducing strategies	Single, in person	Pain intensity (intraoperative, ^a postoperative ^a) Opioid dose (intraoperative, ^a postoperative ^b)
Frenay et al, ²⁸ 2001	Burn pain	30	Hypnosis	Stress reduction	Multiple, in person	Pain intensity (days 1-4 ^b)
Garland et al, ²⁶ 2017	Hospital inpatients reporting intolerable pain or inadequate pain control	244	(1) Hypnotic suggestion, (2) mindfulness training	Pain education	Single, in person	Pain intensity (after treatment ^b) Pain unpleasantness (after treatment ^a) Desire for opioids (after treatment ^a)

(continued)

Table 1. Mind-Body Therapy Study Descriptions (continued)

Source	Clinical Target	No. of Patients	Mind-Body Therapy	Comparator(s)	Session Extensiveness, Format	Pain-Related and Opioid Outcomes (Length of Follow-up)
Ghoneim et al, ⁶⁰ 2000	Dental surgery	60	Hypnosis	Usual care	Single, recording	Pain intensity (postoperative, 1 wk ^b) Opioid dose (postoperative, 1 wk ^b)
Joudi et al, ⁶¹ 2016	Postoperative pain and analgesic use	120	Hypnosis	Usual care	Single, recording	Pain intensity (postoperative ^a) Opioid dose (postoperative ^a)
Lang et al, ⁶² 1996	Interventional radiology procedures	30	Hypnosis	Usual care	Single, in person	Pain intensity (intraoperative ^a) Opioid or sedative dose (intraoperative ^a)
Lang et al, ⁶³ 2000	Arterial, venous, and renal surgery	241	Hypnosis	(1) Structured attention, (2) usual care	Single, in person	Pain intensity (intraoperative ^a) Opioid or sedative dose (intraoperative ^a)
Lang et al, ⁶⁴ 2008	Percutaneous tumor treatment	201	Hypnosis	(1) Empathic attention, (2) usual care	Single, in person	Pain intensity (intraoperative ^a) Opioid or sedative dose (intraoperative ^a)
Mackey et al, ⁶⁵ 2010	Outpatient third molar extraction	91	Hypnosis plus music plus IV sedation	Music plus IV sedation	Single, recording	Pain intensity (24 h postoperative ^a) Opioid dose (24 h postoperative ^a)
Mackey et al, ⁶⁶ 2018	Outpatient third molar extraction	119	Hypnosis plus music plus IV sedation	Music plus IV sedation	Single, recording	Pain intensity (24 h postoperative ^a) Opioid dose (24 h postoperative ^a)
Marc et al, ⁴⁸ 2008	Surgical abortion	350	Hypnosis	Usual care	Single, in person	Pain intensity (intraoperative ^b) Opioid use (yes or no) (intraoperative ^a)
Montgomery et al, ⁶⁷ 2007	Breast surgery	200	Hypnosis	Attention control	Single, in person	Pain intensity (postoperative ^a) Pain unpleasantness (postoperative ^a)
Patterson et al, ³³ 1992	Burn, wound debridement	30	Hypnosis	(1) Attention control, (2) usual care	Single, in person	Pain intensity (postoperative ^a) Opioid dose (postoperative ^b)
Patterson et al, ³⁴ 2010	Hospitalized for traumatic injury	21	VR hypnosis	(1) Usual care, (2) VR distraction	Single, in person	Pain intensity (1 h ^a and 8 h ^a after treatment) Pain unpleasantness (1 h ^a and 8 h ^b after treatment)
Surman et al, ⁶⁸ 1974	Cardiovascular surgery	40	Hypnosis	Usual care	Single, in person	Pain intensity (intraoperative, ^b postoperative ^a) Medication requirements (intraoperative, ^b postoperative ^b)
Syrjala et al, ²⁹ 1992	Cancer pain (undergoing bone marrow transplant)	45	(1) Hypnosis, (2) CBT coping skills	(1) Therapist contact, (2) usual care	Multiple, in person	Pain intensity (1-3 wk after transplant ^b) Opioid dose (1-3 wk after transplant ^b)
Wang et al, ⁶⁹ 2015	Lung cancer surgery	60	Hypnosis plus relaxation plus music	Usual care	Multiple, recording	Pain intensity (4-24 h postoperative ^a) Opioid total dose (4-24 h postoperative ^a) No. of opioid uses (4-24 h postoperative ^a)
Wright et al, ³⁰ 2000	Burn pain	30	Hypnosis	Usual care	Multiple, in person	Pain intensity (burn treatments 1 ^b and 2 ^b) Pain unpleasantness (burn treatments 1 ^a and 2 ^a) Opioid dose (burn treatments 1 ^a and 2 ^a)
Relaxation Studies						
Anderson et al, ⁷⁰ 2006	Cancer pain	57	(1) PMR, (2) positive imagery	(1) Distraction, (2) waitlist	Multiple, recording	Pain intensity (2-9 wk postoperative ^b)
Gavin et al, ³⁷ 2006	Spinal surgery	49	Relaxation	Usual care	Single, in person	Pain intensity (postoperative days 1 ^a and 2 ^a) Opioid dose (postoperative days 1 ^a and 2 ^b)

(continued)

Table 1. Mind-Body Therapy Study Descriptions (continued)

Source	Clinical Target	No. of Patients	Mind-Body Therapy	Comparator(s)	Session Extensiveness, Format	Pain-Related and Opioid Outcomes (Length of Follow-up)
Good, ³⁸ 1995	Abdominal surgery	84	(1) Relaxation, (2) relaxation plus music	(1) Music, (2) usual care	Multiple, recording	Pain intensity (postoperative ^b) Opioid dose (postoperative ^b)
Good et al, ¹⁹ 1999	Abdominal surgery	500	(1) Relaxation, (2) relaxation plus music	(1) Music, (2) attention control	Multiple, recording	Pain sensation (postoperative ^a) Pain distress (postoperative ^a)
Good et al, ⁵⁰ 2010	Abdominal surgery	517	Relaxation plus music	Patient teaching	Single, recording	Pain sensation (postoperative ^a) Pain distress (postoperative ^a) Opioid dose (postoperative ^b)
Haase et al, ⁷¹ 2005	Colorectal cancer surgery	60	(1) Relaxation, (2) guided imagery	Usual care	Multiple, recording	Pain intensity (postoperative ^b) Opioid dose (postoperative ^b)
Konstantatos et al, ³⁵ 2009	Burn wound dressing changes	86	VR relaxation	Usual care	Single, recording	Pain intensity (VR relaxation worse, after dressing change ^a) Opioid dose (after dressing change ^b)
Kwekkeboom et al, ⁷² 2008	Cancer pain during hospitalization	40	(1) PMR, (2) guided imagery	Information	Multiple, recording	Pain intensity (postoperative ^a) Pain-related distress (postoperative ^a)
Mandle et al, ⁷³ 1990	Femoral angiography	45	Relaxation	(1) Music tape, (2) blank tape	Single, recording	Pain rating index (postoperative ^a) Pain intensity (postoperative ^a) Nurse-assessed pain (postoperative ^a) Opioid dose (postoperative ^a)
Manyande et al, ⁷⁴ 1998	Major abdominal or abdominal-perineal surgery	118	Relaxation	Informational tape	Single, recording	Pain intensity (postoperative days 1-7 ^b) Pain distress (postoperative days 1-7 ^a) Intramuscular opioid (intraoperative, ^a postoperative day 1 ^a) Intravenous pump (postoperative day 1 ^a) Recovery opioid (relaxation worse, postoperative ^a) Oral opioid (intraoperative, ^b postoperative 1 d ^b)
Rejeh et al, ³⁶ 2013	Elective abdominal surgery	124	Systematic relaxation	Usual care	Single, recording	Pain intensity (0-12 h postoperative ^a) Opioid dose (6 h postoperative ^a) Opioid use (6 h postoperative ^a)
Roykulcharoen and Good, ²⁴ 2004	Abdominal surgery	102	Systematic relaxation	Lying still in bed	Single, in person	Pain intensity (postoperative ^a) Pain distress (postoperative ^a) Opioid dose (postoperative ^b)
Sloman et al, ⁷⁵ 1994	Cancer pain	67	(1) Relaxation in person, (2) relaxation by tape	Usual care	Multiple, in person plus recording	Present pain intensity (3 wk after discharge ^a) Overall pain intensity (3 wk after discharge ^a) Pain sensation (3 wk ^c) Pain affect (3 wk after discharge ^b) Opioid dose (3 wk after discharge ^b)
Syrjala et al, ³⁹ 1995	Cancer pain	94	(1) Relaxation plus imagery, (2) relaxation plus imagery plus CBT	(1) Therapist contact, (2) usual care	Multiple, in person	Pain intensity (after transplant wk 1-3 ^a) Opioid dose (after transplant wk 1-4 ^b)
Wang et al, ⁴⁰ 2008	Postembolization pain	262	Relaxation plus psychotherapy	Usual care	NR, in person	Pain intensity (postanalgesia ^a)

(continued)

Table 1. Mind-Body Therapy Study Descriptions (continued)

Source	Clinical Target	No. of Patients	Mind-Body Therapy	Comparator(s)	Session Extensiveness, Format	Pain-Related and Opioid Outcomes (Length of Follow-up)
Wilson et al, ⁷⁶ 1981	Surgery, cholecystectomy, and hysterectomy	70	(1) Relaxation, (2) relaxation plus information	(1) Information, (2) usual care	Single, recording	No. of opioid injections (daily after surgery ^a) Pain distress (daily after surgery ^a)
Guided Imagery Studies						
Anderson et al, ⁷⁰ 2006	Cancer pain	57	(1) Positive imagery, (2) PMR	(1) Distraction, (2) waitlist	Single, in person	Pain intensity (2-9 wk after treatment ^a)
Antall et al, ⁷⁷ 2004	Joint replacement surgery	13	Guided imagery	Usual care	Single, recording	Pain intensity (postoperative ^b) Opioid dose (postoperative ^b)
Forward et al, ⁷⁸ 2015	Joint replacement surgery	225	Guided imagery	(1) Massage, (2) usual care	Multiple, in person	Pain intensity (vs usual care, postoperative day 1 ^a) Opioid dose (postoperative day 1 ^a)
Gonzales et al, ⁴² 2010	Head and neck surgical procedures	44	Guided imagery	Usual care	Multiple, recording	Pain intensity (2 h postoperative ^a) Opioid use (2 h postoperative ^b)
Haase et al, ⁷¹ 2005	Colorectal cancer surgery	60	(1) Guided imagery, (2) relaxation	Usual care	Multiple, recording	Pain intensity (postoperative days 1-4 ^b) Opioid use (postoperative days 1-4 ^b)
Kwekkeboom et al, ⁷⁹ 1998	Surgery for breast or gynecologic malignancy	75	Guided imagery	Usual care	Single, recording	Pain intensity (intraoperative, ^b postoperative ^b) Pain distress (intraoperative, ^b postoperative ^b) Pain interference (intraoperative, postoperative ^b)
Kwekkeboom et al, ⁷² 2008	Cancer pain during hospitalization	40	(1) PMR, (2) guided imagery	Information	Multiple, recording	Pain intensity (postoperative ^a) Pain-related distress (postoperative ^a)
Piji et al, ⁴¹ 2016	Laparoscopic cholecystectomy for gall stones	140	Guided imagery	Usual care	Multiple, recording	Pain intensity (postoperative ^b) Opioid use (postoperative ^b)
Tusek et al, ⁸⁰ 1997	Colorectal surgery	130	Guided imagery plus music	Usual care	Multiple, recording	Pain intensity (6 d postoperative ^a) Opioid requirements (6 d postoperative ^a)
Suggestion Studies						
Block et al, ²³ 1991	Heterogeneous sample of anesthetized surgical patients	209	Therapeutic suggestion	Blank tape	Single, recording	Pain intensity (postoperative days 1-7 ^b) Opioid use (postoperative day 8 ^a)
van der Laan et al, ⁸¹ 1996	Gynecologic surgery	60	Therapeutic suggestion	Story control	Single, recording	Pain intensity (24 h postoperative ^b) Opioid dose (24 h postoperative ^b)
Melzack et al, ⁴⁹ 1996	Surgery, cholecystectomy and hysterectomy	20	Positive suggestion plus music	Scientific information plus music	Single, recording	Pain intensity (postoperative days 1-4 ^b) Opioid intake (postoperative days 1-4 ^b)
McLIntock et al, ⁸² 1990	Hysterectomy surgery	63	Positive suggestion	Blank tapes	Single, recording	Pain intensity (0-24 h postoperative ^b) Opioid dose (0-24 h postoperative ^b)
Nilsson et al, ⁴³ 2001	Abdominal surgery	90	Therapeutic suggestion plus music	(1) Music, (2) operating sounds	Single, recording	Pain intensity (postoperative ^b) Pain unpleasantness (postoperative ^b) Opioid dose (postoperative ^b)
Nilsson et al, ⁸³ 2003	Varicose vein or open inguinal hernia repair surgery	182	Therapeutic suggestion plus music	(1) Music alone, (2) blank tape	Single, recording	Pain intensity (postoperative ^b) Opioid dose (postoperative ^b)

(continued)

Table 1. Mind-Body Therapy Study Descriptions (continued)

Source	Clinical Target	No. of Patients	Mind-Body Therapy	Comparator(s)	Session Extensiveness, Format	Pain-Related and Opioid Outcomes (Length of Follow-up)
Jamison et al, ⁴⁴ 2010	Chronic back and/or neck pain and history of or high risk for prescription opioid misuse	62	Cognitive behavioral substance misuse counseling	Usual care	Multiple, in person	Pain intensity (6 mo ^a) Pain interference (6 mo ^b) Pain disability (6 mo ^b) Opioid misuse (6 mo ^a)
Kroenke et al, ⁸⁴ 2009	Comorbid chronic musculoskeletal pain and depression (opioid users analyzed separately)	134	Pain self-management	Usual care	Multiple, in person	Opioid use (12 mo ^b)
Naylor et al, ⁸⁵ 2010	Chronic musculoskeletal pain (opioid users analyzed separately)	32	Group CBT followed by therapeutic interactive voice response	Group CBT followed by usual care	Multiple, in person plus recording	Opioid use (4 mo ^a and 8 mo ^a)
Rolvig et al, ⁸⁶ 2016	Undergoing lumbar spinal fusion for degenerative spinal disorders	90	Preoperative CBT	Usual care	Multiple, in person	Pain intensity (posttransplant days 1-7 ^b) Mobility (posttransplant days 1-3 ^a) Opioid use beyond standard protocol (posttransplant day 2 ^a)
Syrjala et al, ²⁹ 1992	Cancer pain (undergoing bone marrow transplant)	45	(1) CBT coping skills, (2) hypnosis	(1) Therapist contact, (2) usual care	Multiple, in person	Pain intensity (postoperative weeks 1-3 ^a) Opioid dose (postoperative weeks 1-3 ^b)
Syrjala et al, ³⁹ 1995	Cancer pain	94	(1) Relaxation plus imagery, (2) relaxation plus imagery plus CBT coping skills	(1) Therapist contact, (2) usual care	Multiple, in person	Pain intensity (posttreatment weeks 1-3 ^a) Opioid dose (posttransplant wk 1-4 ^b)
Wilson et al, ⁴⁵ 2016	Chronic noncancer pain plus prescribed opioids	92	Internet-based pain self-management	Usual care	Multiple, recording (online self led)	Pain intensity (8 wk ^b) Pain interference (8 wk ^b) Opioid misuse (8 wk ^a) Opioid use decrease or stop (8 wk ^a)

Abbreviations: CBT, cognitive-behavioral therapy; EMA, ecologic momentary assessment; IV, intravenous; NR, not reported; PMR, progressive muscle relaxation; VR, virtual reality.

^a Statistically significant between-groups difference favoring the mind-body therapy over the control condition

^b Nonsignificant between-groups difference.

(eFigure 1 in the [Supplement](#)), with homogeneity of effect sizes ($Q [\chi^2 = 4.59, P = .10]; I^2 = 56.20\%$).

Association of Meditation With Opioid-Related Outcomes

Four of the 5 studies (80%) reported significant improvements in opioid misuse,²⁵ opioid craving,^{25,26} time to opioid cessation,⁵⁵ and/or opioid use²⁷; 1 of these studies reported reduced opioid analgesic use,²⁷ but the analgesic outcome was an imprecise categorical variable. One study⁵⁷ failed to find effects on opioid dose, and 2 other studies^{25,26} were unable to consistently and reliably collect opioid dosing data.

Intervention Characteristics and Clinical Pain Targets

Three of the 5 studies (60%) examined multiple-session mindfulness-based interventions: Mindfulness-Oriented Recovery Enhancement,²⁵ meditation-based CBT,⁵⁷ and Mindfulness-Based Stress Reduction.²⁷ Two studies examined single-session interventions: mindful breathing²⁶ and Acceptance and Commitment Therapy with meditation.⁵⁵ Four of the 5 studies^{25,27,55,57} (80%) focused on chronic pain conditions.

Hypnosis Studies

Association of Hypnosis With Pain Outcomes

Fifteen of the 23 hypnosis studies^{26,29-31,33,34,47,61-67,69} (65%) reported statistically significant improvements in pain intensity, pain unpleasantness, and/or pain affect. Meta-analytic results indicated that hypnosis had a significant moderate association with pain reduction (Cohen $d = -0.54$; 95% CI, -0.87 to -0.20 ; $P < .001$) (eFigure 2 in the [Supplement](#)), with some heterogeneity of effect sizes ($Q [\chi^2 = 38.16, P < .001]; I^2 = 73.90\%$).

Association of Hypnosis With Opioid-Related Outcomes

Twelve hypnosis studies^{26,30,46,59,61-66,69} (63%) reported statistically significant improvements in opioid dose, desire for opioids, and/or time to first postoperative opioid dose.

Intervention Characteristics and Clinical Pain Targets

Four studies^{28-30,69} (17%) examined multiple-session hypnotic interventions, with the remainder^{26,31-34,46-48,58,68} examining single-session hypnotic inductions. Seventeen studies^{29,34,46-48,58-69} focused on presurgical, postsurgical, or procedural pain; 5 studies focused^{28,30-33} on burn pain; and 1 study²⁶ focused on acute pain.

Relaxation Studies

Association of Relaxation With Pain Outcomes

Twelve of the 16 relaxation studies^{19,24,36,37,39,40,50,72-76} (75%) reported statistically significant improvements in pain intensity or severity, pain sensation, pain distress, and/or nurse-assessed pain. In 1 study,³⁵ pain intensity was reported as significantly worse in a virtual reality relaxation group compared with a morphine-only comparison group during burn dressing change. Meta-analytic results indicated that relaxation did not have a significant association with pain reduction (Cohen $d = -0.45$; 95% CI, -1.13 to 0.22 ; $P = .19$) (eFigure 3 in the [Supplement](#)), with some heterogeneity of effect sizes ($Q [\chi^2 = 218.62, P < .001]; I^2 = 96.96\%$).

Association of Relaxation With Opioid-Related Outcomes

Three studies^{36,73,74} (19%) reported significant therapeutic effects of relaxation on procedural opioid dose, postoperative opioid dose, and number of patients receiving opioids. Two studies (14%) reported significantly worse opioid-related outcomes, including postoperative opioid dose³⁷ and recovery dose.⁷⁴

Intervention Characteristics and Clinical Pain Targets

Seven studies^{19,38,39,71,72,75} examined multiple-session relaxation interventions, with the remainder^{24,35-37,40,50,73,74,76} examining single-session relaxation interventions and 1 study⁴⁰ not reporting that information. Relaxation interventions included progressive muscle relaxation, systematic relaxation, and jaw relaxation. Eleven studies^{19,24,36-38,40,50,71,73,74,76} focused on surgical or procedural pain, 4 studies^{39,70,72,75} focused on cancer pain, and 1 study³⁵ focused on burn dressing change pain.

Guided Imagery Studies

Association of Guided Imagery With Pain Outcomes

Three of the 9 guided imagery studies^{72,78,80} (33%) reported statistically significant improvements in pain intensity. There were insufficient numbers of guided imagery studies with pain values to perform a meta-analysis.

Association of Guided Imagery With Opioid-Related Outcomes

Two studies^{41,80} (29%) reported statistically significant effects of guided imagery on opioid dose.

Intervention Characteristics and Clinical Pain Targets

Six studies^{41,42,71,72,78,80} examined multiple-session guided imagery interventions, with the remainder^{70,77,79} examining single-session interventions. Seven studies^{41,42,71,77-80} focused on surgical pain, and 2 studies^{70,72} focused on cancer pain.

Therapeutic Suggestion Studies

Association of Suggestion With Pain Outcomes

Two of the 6 therapeutic suggestion studies^{23,83} (33%) reported statistically significant improvements in pain intensity. No other studies reported comparative improvements in pain outcomes, including pain intensity or pain unpleasantness. Meta-analytic results indicated that suggestion had a significant moderate association with pain reduction (Cohen $d = -0.68$; 95% CI, -1.18 to -0.18 ; $P = .008$) (eFigure 4 in the [Supplement](#)), with some heterogeneity of effect sizes ($Q [\chi^2 = 5.75, P = .056]; I^2 = 63.66\%$).

Association of Suggestion With Opioid-Related Outcomes

Three studies^{23,43,82} (50%) reported significant therapeutic effects of suggestion on opioid dose.

Intervention Characteristics and Clinical Pain Targets

All 6 studies^{23,43,49,81-83} examined single-session, audio-recorded suggestions and focused on surgical pain.

CBT Studies

Association of CBT With Pain Outcomes

Three studies^{29,39,44} (43%) reported statistically significant improvements in pain intensity. One study⁸⁶ (14%) reported sta-

tistically significant improvements in postoperative mobility. No other studies reported comparative improvements in pain outcomes including pain intensity or pain disability. Meta-analytic results indicated that CBT had a significant moderate association with pain reduction (Cohen $d = -0.43$; 95% CI, -0.71 to -0.15 ; $P = .002$) (eFigure 5 in the Supplement), with homogeneity of effect sizes ($Q [\chi^2 = 2.07, P = .55]; I^2 = 0.0\%$).

Association of CBT With Opioid-Related Outcomes

Four of the 7 CBT studies^{44,45,85,86} (57%) reported significant therapeutic effects of CBT on opioid dose, use, or misuse.

Intervention Characteristics and Clinical Pain Targets

All 7 studies^{29,39,44,45,84-86} of CBT interventions examined multiple-session CBT interventions. Interventions used in-person therapists,^{29,39,44,86} pain self-management,^{45,84} and interactive voice response.⁸⁵ Four studies^{44,45,84,85} focused on chronic pain, 2 studies^{29,39} focused on cancer pain, and 1 study⁸⁶ focused on surgical pain.

Overall Meta-analysis

Characteristics of the Overall Meta-analysis

Two meta-analyses were performed on all studies for which data could be extracted to determine the association of MBTs with reduced pain and opioid use. Inspection of Baujat plots (eFigure 6 in the Supplement) revealed that 2 studies,^{23,24} both of which demonstrated significant clinical efficacy in favor of MBTs, were appropriate for removal as outliers: 1 in the pain meta-analysis and 1 in the opioid use meta-analysis. We chose to remove those studies to obtain stable and reliable meta-analytic effect size estimates per best practice guidelines.⁸⁷

Pain-Related Outcome Results

Overall, MBTs had a significant, moderate association with reduced pain (Cohen $d = -0.51$; 95% CI, -0.76 to -0.27 ; $P < .001$) (Figure 2A). Computation of the $Q (\chi^2 = 287.21, P < .001)$ and I^2 (90.53%) statistics showed some heterogeneity of effect sizes. These data were derived from 29 studies ($n = 2916$), with 1679 patients receiving an MBT. A funnel plot (eFigure 7 in the Supplement) and the Egger statistic ($z = -0.65, P = .52$) did not indicate publication bias.

Opioid-Related Outcome Results

Overall, MBTs had a significant, small association with opioid use (Cohen $d = -0.26$; 95% CI, -0.44 to -0.08 ; $P = .01$) (Figure 2B). Computation of the $Q (\chi^2 = 6.70, P = .82)$ and I^2 (0.0%) statistics showed homogeneity of effect sizes. These data were derived from 8 distinct studies ($n = 435$), with 250 patients receiving an MBT. A funnel plot (eFigure 8 in the Supplement) and the Egger statistic ($z = -0.30, P = .76$) did not indicate publication bias.

Discussion

To our knowledge, this study represents the first systematic evaluation of the therapeutic benefits of MBTs for opioid-treated clinical pain in studies including more than 6000 pa-

tients. Overall meta-analytic results revealed that MBTs had a statistically significant, moderate association with reduced pain intensity and a statistically significant, small association with reduced opioid dosing compared with a range of control arms. The strength of the evidence for the therapeutic effects of MBTs on pain and opioid dose reduction was moderate, although this evidence varied by specific MBT. Taken together with descriptive results from this systematic review, MBTs overall may be associated with improved pain and opioid-related outcomes for a variety of painful health conditions. Most studies used active or placebo controls and had low risk of bias (Figure 3 and eFigures 9-14 in the Supplement), increasing confidence that the reported benefits are not solely the result of nonspecific therapeutic factors.

From a more granular perspective, differences emerged regarding the efficacy of the specific types of MBTs studied. Most studies of meditation, hypnosis, and CBT reported significant therapeutic associations with opioid-related outcomes, including opioid dosing, craving, and opioid misuse, whereas comparatively fewer studies of suggestion, imagery, and relaxation reported significant associations with opioid-related outcomes. Of note, 2 studies^{37,74} reported significantly worsened opioid dosing outcomes after relaxation, suggesting the possibility of adverse effects. However, few studies reported adverse effects or harms of MBTs. Because of insufficient statistical power from the paucity of studies reporting opioid dose data, we could not conduct separate meta-analyses for each type of MBT on opioid dosing.

A different pattern emerged with regard to pain outcomes. Separate meta-analyses by specific MBT type demonstrated significant associations of meditation, hypnosis, CBT, and suggestion with pain outcomes, with the largest effect sizes observed for meditation studies. Differences in therapeutic efficacy between MBTs could be ascertained through rigorous comparative effectiveness trials. Although several of the studies^{26,29,39,70-72} in this review compared 2 MBTs, they were not sufficiently powered to detect what are likely to be small effect size differences between bona fide treatments. Furthermore, many of the MBTs reviewed involved combinations of approaches, including some with CBT. Dismantling trials could unpack multimodal MBTs and determine the differential effects of their various treatment components.

Differences also emerged with regard to foci of MBT clinical pain targets. Most of the meditation-based intervention studies focused on treating chronic noncancer pain (eg, low back pain). In contrast, most hypnosis, relaxation, imagery, and suggestion studies focused on treating acute, procedural, or cancer-related pain. It is plausible that MBTs have differential associations with acute vs chronic pain as well as opioid use depending on their mechanisms of action. In that regard, mindfulness training aims to increase acceptance, decrease catastrophizing, and facilitate a shift from affective to sensory processing of pain sensations by reappraising pain as innocuous sensory information rather than an emotionally laden threat to bodily integrity.⁸⁸ These mechanisms might be especially efficacious for chronic pain conditions in which pain exacerbation occurs through the development of cognitive schemas, attentional hypervigilance,

Figure 2. Summary of Studies Examining the Association of Mind-Body Therapies With Pain and Opioid Use

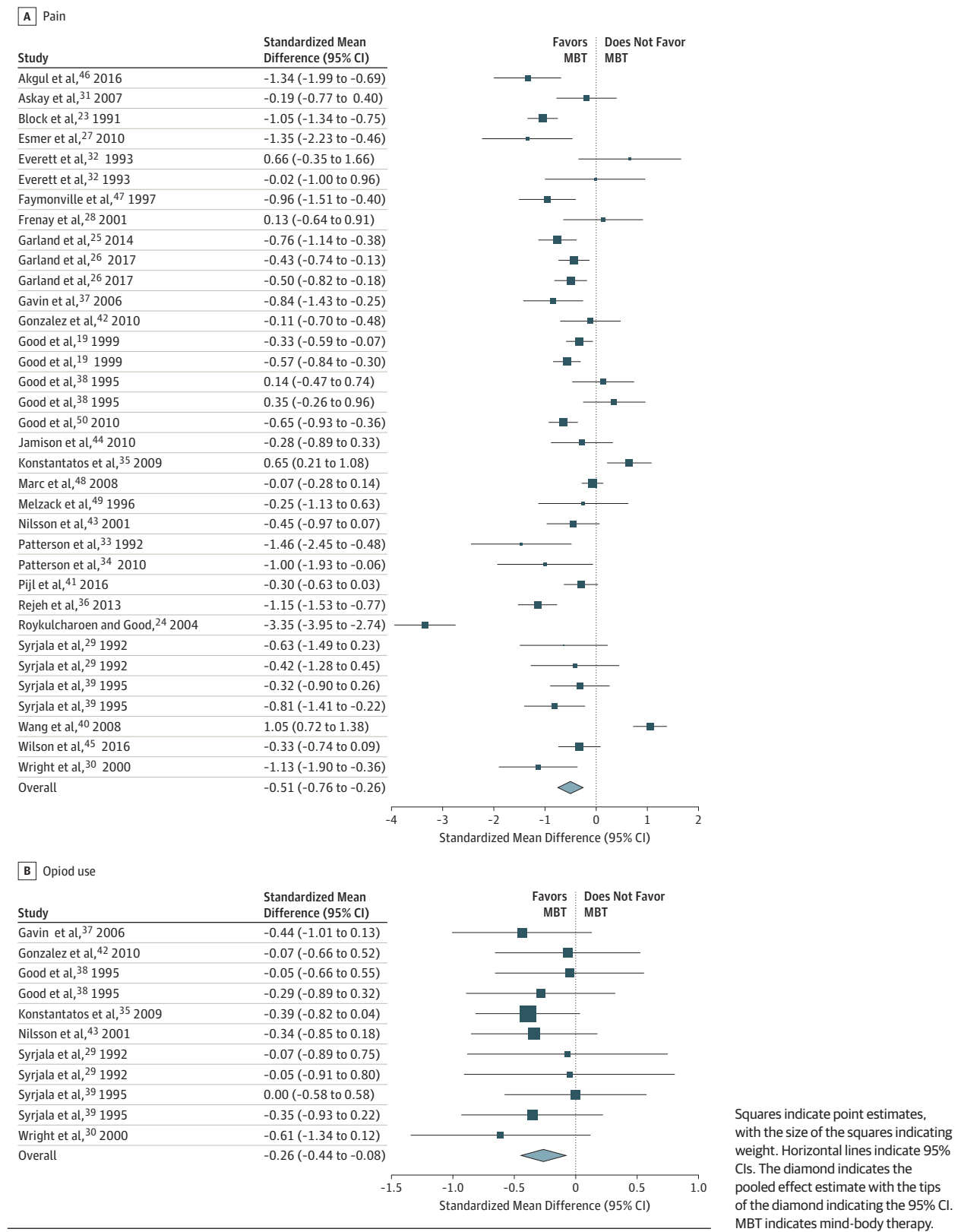
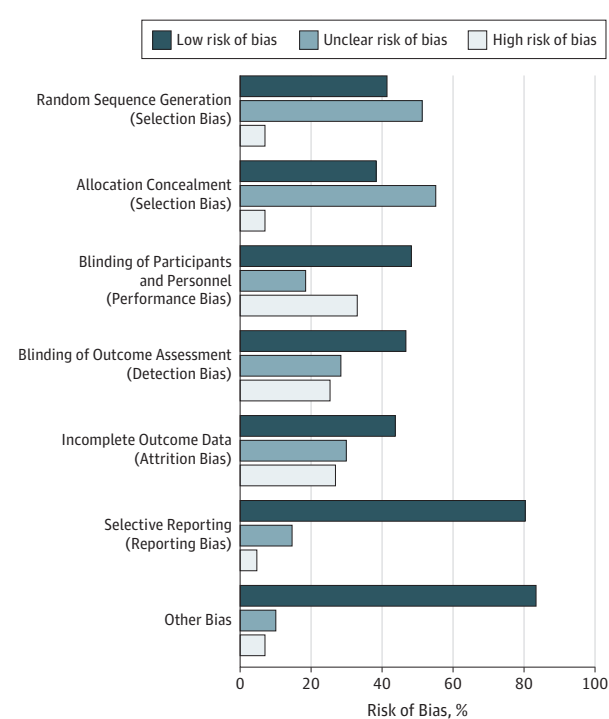


Figure 3. Risk of Bias



Present review authors' judgments about each risk of bias item presented as percentages across all included studies.

and distress intolerance. In contrast, techniques such as hypnosis and guided imagery aim to reduce pain through dissociation or imaginal superimposition of pleasurable sensations onto the painful body part.⁸⁹ These mechanisms might instead be efficacious for acute pain conditions or procedural pain where nociceptive peripheral or visceral afference during noxious stimulation causes suffering. However, mindfulness and hypnosis appear to help alleviate pain via corticothalamic modulation of ascending nociceptive input.⁹⁰⁻⁹³ Additional studies are needed to disentangle the unique and overlapping mechanisms of MBTs.

Recommendations for future research are detailed in Table 2. Future studies should collect data needed to obtain quantitative estimates of opioid dosing, including opioid type, dose per unit, dosage form, dosage frequency, and duration of use. Because participant self-report is unreliable, if possible, data should be extracted from electronic health records and prescription drug monitoring programs. Trials that examine the effect of MBT on opioid misuse should triangulate data from self-reports, practitioner evaluation, and toxicologic screening. Psychophysiologic measures could also be used to assess the association of MBT with opioid cue reactivity, and such measures have been reported to be sensitive to the use of MBTs in patients with opioid-treated pain.^{56,94}

Extant evidence from controlled trials suggests that MBTs can improve clinical pain and opioid-related outcomes. Practitioners should consider presenting MBTs as nonpharmacologic adjuncts to opioid analgesic therapy. The observed findings on procedural pain are especially notable; if MBTs can reduce pro-

Table 2. Limitations of Existing Studies of MBTs and Suggestions for Future Research in this Area

Limitations of Existing Studies	Suggestions for Future Research
Insufficient reporting of opioid dosing outcomes	Record the type of opioid agent prescribed, the dose per unit, the dose form, dose frequency, and duration of opioid use
Outcomes for opioid-using subgroups were not analyzed separately in the results	Conduct a priori subgroup analyses for opioid users in future clinical trials
High levels of intervention heterogeneity preclude examination of effect modifiers, including intervention dosage and delivery format	Increase the number of studies of each type of MBT of various dosages (brief vs multiweek MBT) and delivery formats (delivered in person by practitioner vs audio recording or internet); randomly assign participants to different MBT dosages and delivery formats
High levels of heterogeneity in study design preclude determinations of the durability of treatment effects	Use standardized and consistent assessment points and outcome measures to facilitate meta-analytic comparisons across studies
Some studies have small sample sizes	Increase sample size to ensure full power to detect treatment effects
Some studies had risk of bias because of a lack of blinding of participants, personnel, and assessors	Blind participants, personnel, and assessors, as well as use double-blind or active placebo-controlled designs whenever possible
Some studies had risk of bias because of a lack of intent-to-treat analysis	Use intent-to-treat analyses to assess primary and secondary outcomes
Some studies relied on self-report of opioid dosing or opioid misuse-related outcomes	Triangulate data from self-reports, practitioner evaluation, PDMPs, and urine toxicologic screenings via modeling strategies capable of analyzing latent dependent variables composed of multiple observed indicators (eg, structural equation modeling); use psychophysiologic testing to detect addictive tendencies toward opioids

Abbreviations: MBT, mind-body therapy; PDMPs, prescription drug monitoring plans.

cedural pain, they may serve as an important form of primary prevention of long-term opioid use and OUD. Among MBTs, meditation-based interventions and CBT may be particularly useful given their association with reduced pain severity and functional interference, their potential to improve opioid-related outcomes, their broad public appeal, and the comparatively larger numbers of practitioners already trained to deliver these modalities. These interventions may also increase patient self-efficacy in that they involve developing self-management skills that patients can use independently after an initial brief training period. Moreover, because MBTs can be delivered via audio-recorded formats and in person by social workers and nurses for relatively low cost, they may prove to have a significant economic advantage in future cost-effectiveness research. Behavioral health care professionals working alongside physicians could feasibly integrate MBTs into standard medical practice through coordinated care management, colocated care on site with some system integration, or a fully integrated, onsite care model (eg, behavioral health integration into primary care). Insofar as MBTs are associated with pain relief and opioid use reduction among patients prescribed opioids for a range of pain conditions, MBTs may help alleviate the opioid crisis.

Limitations

This study has limitations. We could not draw quantitative conclusions about outcome modifiers, such as dose or delivery format, or about durability of treatment effects because of high levels of study heterogeneity. Outcomes ranged from immediate postintervention acute pain outcomes to outcomes that lasted 3 months or longer. Approximately one-third of studies had small samples and therefore may have been underpowered. Although most studies had low risk of bias, a number of trials had biases, such as lack of blinding of participants, personnel, and/or outcomes assessors, and lack of intention-to-treat analysis. Given that nearly approximately half of the trials reviewed were conducted before publication of the revised CONSORT statement in 2001,⁹⁵ some studies were missing clinical trial reporting information. Funnel plots and the Egger statistic indicated some publication bias for meditation and suggestion studies.

Another limitation was the insufficient reporting of opioid dosing in the MBT literature. A number of studies, including high-impact trials,⁹⁶ could not be included because the type of analgesic was unspecified and/or outcomes for opioid users were not analyzed separately. Of the trials reviewed, less than one-fifth yielded opioid dosing data of sufficient detail to be meta-analyzed.

Conclusions

The findings suggest that MBTs are associated with moderate improvements in pain and small reductions in opioid dose and may be associated with therapeutic benefits for opioid-related problems, such as opioid craving and misuse. Future studies should carefully quantify opioid dosing variables to determine the association of mind-body therapies with opioid-related outcomes.

ARTICLE INFORMATION

Accepted for Publication: August 29, 2019.

Published Online: November 4, 2019.
doi:10.1001/jamainternmed.2019.4917

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Supervision: Garland.

Conflict of Interest Disclosures: Dr Garland reported serving as the director of the Center on Mindfulness and Integrative Health Intervention Development, which provides

Mindfulness-Oriented Recovery Enhancement (MORE), mindfulness-based therapy, and cognitive behavioral therapy in the context of research trials for no cost to research participants; receiving honoraria and payment for delivering seminars, lectures, and teaching engagements (related to training practitioners in MORE and mindfulness) sponsored by institutions of higher education, government agencies, academic teaching hospitals, and medical centers; and receiving royalties from the sale of books related to MORE during the conduct of the study Dr Keefe reported a patent pending. No other disclosures were reported.

Funding/Support: Dr Garland was supported by grants R01DA042033 and R61AT009296; Dr Brintz was supported by grant T32AT003378; Dr Roseen was supported by grant F32AT009272; and Dr Keefe was supported by grants R34DA040954, R01NR013910, and UG3AT009790 from the National Institutes of Health during the preparation of the manuscript.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Additional Contributions: Emilee Naylor, BA, independent research coordinator, assisted with the literature search for an early version of the manuscript. She was compensated for her work.

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