General Section
Review

OPEN

PAIN REPORTS®

Systematic scoping review of interactions between analgesic drug therapy and mindfulness-based interventions for chronic pain in adults: current evidence and future directions

Rex Park[a], Mohammed Mohiuddin[a], Patricia A. Poulin[b,c,d], Tim Salomons[e,f], Robert Edwards[g], Howard Nathan[d], Chris Haley[a], Ian Gilron[a,h,f,i,*]

Abstract

Most patients with chronic pain do not find adequate pain relief with a single treatment, and accumulating evidence points to the added benefits of rational combinations of different treatments. Given that psychological therapies, such as mindfulness-based interventions (MBIs), are often delivered in conjunction with concomitant analgesic drug therapies (CADTs), this systematic scoping review examines the evidence for any interactions between MBIs and CADTs. The protocol for this review has been published and registered. MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and PsycINFO databases were searched until July 2019. We included randomized controlled trials that evaluated the efficacy of MBIs for the treatment of chronic pain. A total of 40 randomized controlled trials (2978 participants) were included. Thirty-nine of 40 (97.5%) included mindfulness-based clinical trials allowed the use of CADTs. However, only 6 of these 39 (15.4%) trials provided adequate details of what these CADTs were, and only 4 (10.3%) trials controlled for CADTs. Of great relevance to this review, none of the included trials analyzed the interactions between MBIs and the CADTs to determine whether they have an additive, synergistic, or antagonistic effect on chronic pain. Adverse events were inconsistently reported, and no judgment could be made about safety. Future trials assessing the interactions between MBIs and CADTs, with better harms reporting, are needed to better define the role of MBIs in the management of chronic pain.

Keywords: Chronic pain, Mindfulness, Analgesic therapy, Clinical trials, Systematic review, Meditation

1. Introduction

Chronic pain is a multidimensional health condition generally described as pain that persists for over 3 months.[77] Chronic pain is estimated to affect 1.5 billion individuals worldwide and cost the United States up to $635 billion per year when direct healthcare and productivity costs are considered.[9,13,17,33,53] Chronic pain is also one of the leading causes of human suffering and disability in the world and has major negative impacts on work-related outcomes.[3,76]

Pain is rarely managed effectively with pharmacological agents because of limited efficacy and dose-limiting adverse effects, leaving a significant unmet need for sufferers.[36,54] However, despite the limited evidence supporting the effectiveness and safety of opioids for chronic pain, they have been the mainstay of treatment for chronic pain in the United States for the past 2 decades. The common practice of prescribing opioids for chronic pain has been associated with increases in opioid misuse and opioid-related mortality.[1,36]

Mindfulness-based interventions (MBIs) for the management of chronic pain have received considerable attention in the past 3 decades because of emerging evidence regarding their efficacy and safety.[43,55,68,88] Mindfulness-based interventions for chronic health problems involve multiple components, which can include

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Department of Anesthesiology and Perioperative Medicine, Kingston General Hospital, Queen's University, Kingston, ON, Canada, [b] Department of Psychology, The Ottawa Hospital, Ottawa, ON, Canada, [c] Clinical Epidemiology, The Ottawa Hospital Research Institute, Ottawa, ON, Canada, [d] Department of Anesthesiology and Pain Medicine, University of Ottawa, Ottawa, ON, Canada, [e] Department of Psychology, Queen's University, Kingston, ON, Canada, [f] Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada, [g] Department of Anesthesiology, Harvard University, Cambridge, MA, USA, [h] Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON, Canada, [i] School of Policy Studies, Queen's University, Kingston, ON, Canada

**Corresponding author. Address: Department of Anesthesiology and Perioperative Medicine, Kingston General Hospital, Queen's University, Kingston, ON, Canada. Tel.: 1-613-549-6666 ext 3963. E-mail address: gilroni@queensu.ca (I. Gilron).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painrpts.com).

Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of The International Association for the Study of Pain. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0 (CC BY-ND) which allows for redistribution, commercial and noncommercial, as long as it is passed along unchanged and in whole, with credit to the author.

PR9 5 (2020) e868

http://dx.doi.org/10.1097/PR9.0000000000000868

systematic meditation training, patient education, yoga exercises, and group dialogue.[55] Mindfulness, the core component of MBIs, involves learning to purposefully and nonjudgmentally observe one's own thoughts, feelings, and sensations in the present moment without attempting to change them.[47]

A substantial body of evidence supports the possible benefits of MBIs for patients with chronic pain, such as its positive effects on distress, functioning, and quality of life.[43,55,68] A recent systematic review with 38 randomized controlled trials (RCTs) demonstrated that mindfulness interventions resulted in significant improvements in chronic pain, depression, and quality of life, which are consistent to the findings of previous reviews in this area.[43] However, the weakness in the body of evidence precluded any strong conclusions. Although mindfulness may reduce pain intensity directly, the primary goal of mindfulness is to improve functioning and quality of life and minimize distress.[68] Mindfulness-based interventions for chronic pain are guided by the principle that the practice of mindfulness results in an attenuation of coupling between the sensory component of pain and the cognitive and emotional components of pain.[47] Aligned with this principle, recent research demonstrates neural mechanisms that support mindfulness-based pain reduction, with mindfulness affecting areas of the brain related to attention, introspection, and emotional processing.[40,87] The cognitive and emotional components can amplify pain, contribute to the development of depression and anxiety, and contribute to the avoidance of activity, thereby exacerbating disability.[8] Diminishing the cognitive and emotional reactions to chronic pain through mindfulness is believed to reduce emotional distress and thus reduce suffering and disability.[8]

The experience of pain is influenced by biology, beliefs, culture, mood, anxiety, and the environment. As a result, a biopsychosocial approach that addresses the multiple dimensions of chronic pain is considered the "gold standard." It is now common for chronic pain to be managed through the integration of various treatment modalities in an individualized patient-specific fashion.[34,48,51,57] However, the body of evidence to support the rational use of specific treatment combinations is quite limited.[36] The combined use of MBIs and analgesic drugs could provide added benefit, but there have been no reports of interaction effects of the combination of MBIs with any specific analgesic drugs. Thus, we performed a systematic scoping review to evaluate mindfulness-based trials for chronic pain to determine which concurrent drug therapies were used during each trial and look at the evidence for the efficacy and safety of combining MBIs with analgesic drugs compared with monotherapy.

2. Objectives

The objectives of this review are to examine clinical trials of MBIs for chronic pain with respect to concomitant drug therapy, evaluate the available evidence on the interactions between MBIs and various drug treatments, and assess harms of MBIs.

3. Methods

The review protocol has been previously published,[63] registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=150576) and prepared in accordance with recommendations specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[58]

3.1. Sources of evidence

We searched MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and PsycINFO from their inception until July 2019. The search strategy included terms only related to the health condition (chronic pain) and intervention (mindfulness) to ensure a sensitive search strategy. The search excluded studies that were not published in English. The search strategies for MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and PsycINFO are provided in Supplemental Appendix 1 (available at http://links.lww.com/PR9/A87).

We also reviewed the bibliographies of the RCTs included in our review, as well as searched clinical trial databases (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform, to identify additional published or unpublished data.

3.2. Types of studies

We included RCTs that evaluated the efficacy of MBIs in the treatment of chronic pain. Studies with less than 10 participants were excluded to minimize small study bias.

3.3. Types of participants

Studies of adults (older than 18 years) reporting any type of chronic pain for at least 3 months were included in the review. Chronic pain could include persistent (eg, fibromyalgia) and recurrent (eg, migraine) pain.

3.4. Types of interventions

We focused on MBIs administered for the treatment of chronic pain. To provide a discrete set of results and to summarize the current state of the mindfulness trials with respect to concomitant drug therapy, we focused on "mindfulness," "mindfulness-based stress reduction," "mindfulness-oriented recovery enhancement," "mindfulness-based cognitive therapy," "mindfulness meditation," "mindfulness awareness in body-oriented therapy," or any intervention that is a modification of these mindfulness-based therapies. We excluded studies in which mindfulness is only a component of the intervention (eg, physical-cognitive-mindfulness-training). Studies using any type of concomitant analgesic drug therapies (CADTs) for the treatment of chronic pain were eligible for inclusion in this review.

3.5. Comparators

We included studies that compared MBIs with usual care, wait-list control, or an active comparator.

3.6. Primary outcomes

Our primary outcomes were the following: (1) what CADTs the trial participants were receiving, (2) if and how trials controlled for what CADTs the participants were receiving, and (3) if trials analyzed the interaction between the MBI and the CADTs the trial participants were receiving. For the trials that analyzed the interaction between mindfulness and drug therapy, we planned to look at what the results were in terms of pain intensity and pain relief (eg, MBI plus concomitant drug therapy compared with only concomitant drug therapy in the control group in reducing pain intensity).

3.7. Secondary outcomes

Secondary outcomes included how MBIs plus concomitant drug treatment differed from only drug therapy in the control group in managing secondary features of chronic pain including depression, physical and mental health-related quality of life, and functional disability. Secondary outcomes also included participants reporting any or serious adverse events.

3.8. Data collection and analysis

Two authors (R.P. and M.M.) independently evaluated citation titles and abstracts for inclusion using Covidence software (www.covidence.org). Both authors were required to be in agreement for inclusion. We excluded studies that clearly did not satisfy our inclusion criteria, and full-text screening was performed on the remaining studies. Disagreements between the authors were resolved by discussion and consensus and, if necessary, resolution by a third author (I.G.). A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of this process is provided (**Fig. 1**).

3.9. Data extraction and management

Two review authors (R.P. and M.M.) extracted data for primary and secondary outcomes independently. Disagreements between the reviewers were resolved by discussion and consensus. Other data, such as study characteristics, were extracted by one author (R.P.). Data extracted from each citation included information about the study design, trial duration, follow-up time, pain condition studied, participant inclusion and exclusion criteria, number of participants included, number of dropouts, details of the MBI, if and how adherence to the intervention was measured, primary and secondary outcome measures, and other study results.

3.10. Assessment of risk of bias in included studies

For each study included in the review, risk of bias was assessed using criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. We assessed the following for each study:

1. (1) Random sequence generation for possible selection bias: The method used to generate the allocation sequence was scored at a high risk of bias if they used a nonrandom process (eg, odd or even date of birth), unclear risk of bias if the method used was not clearly stated, or low risk of bias if they used a truly random process (eg, computer random number generator).
2. (2) Allocation concealment for possible selection bias: The method used to conceal allocation to interventions before assignments was scored at a high risk of bias if they did not conceal allocation (eg, open list), unclear risk of bias if the

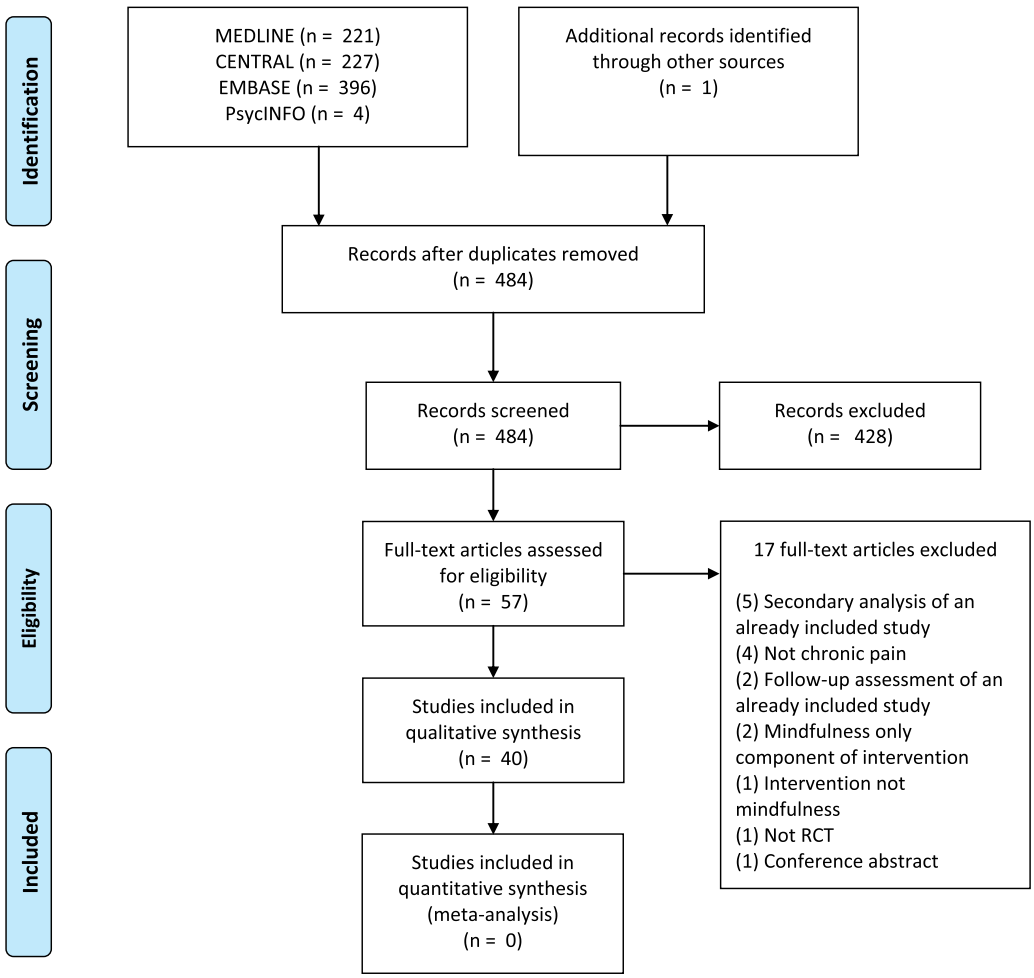

Figure 1. Study flow diagram. RCT, randomized controlled trial.

method was not clearly stated, and low risk of bias if they used methods where allocation could not have been foreseen (eg, consecutively numbered sealed opaque envelopes).
3. Blinding of participants and personnel for possible performance bias: The method used to blind study personnel and participants was scored at a high risk of bias if the personnel and participants were not blinded or the study did not mention they were blinded, unclear if the study stated they were blinded but did not provide an adequate description of how it was achieved, and low risk of bias if the study described the method used to achieve blinding (eg, identical study drugs).
4. Blinding of outcome assessment for possible detection bias: The method used to blind study outcome assessors from knowledge of which intervention a participant received was scored at a high risk of bias if the study was not blinded, unclear risk of bias if it was unclear how blinding was achieved, and low risk of bias if the study clearly stated the assessors were unaware of treatment allocation (and ideally described how this was performed).
5. Incomplete outcome data for possible attrition bias: The method used for handling incomplete data was scored as a high risk of bias if they used a completer analysis or had a high dropout rate (>25%), unclear risk of bias if they used last-observation-carried-forward analysis or had a >10% dropout rate (but <25% dropout rate), and low risk of bias if they used baseline observation carried forward analysis, used multiple imputations, or had a <10% dropout rate.
6. Selective reporting for possible reporting bias: We scored the risk of reporting bias as a high risk of bias if the prespecified outcomes of interest were not reported, unclear risk of bias if there was any anomaly in reporting (eg, some outcomes not participant-reported), and low risk of bias if it was clear that all prespecified and expected outcomes of interest were reported.
7. The size of the study for possible biases confounded by the small sample size: The size of the study category was scored at a high risk of bias if the study had less than 50 participants per treatment arm, unclear risk of bias if the study had 50 to 200 participants per treatment arm, and low risk of bias if the study had greater than 200 participants per treatment arm.

3.11. Analysis of outcomes

A descriptive approach was used to report the primary outcomes because the outcomes were expected to likely be varied across studies. We planned to use a descriptive approach to evaluate how combination treatments differ from monotherapy in managing secondary features of chronic pain such as depression, physical and mental health-related quality of life, and functional disability. We planned to evaluate the interactions between MBIs and drug therapy to the degree that each trial accounted for the drug effects. However, the interactions between MBIs and drug therapy were not analyzed in any of the included studies.

3.12. Dealing with missing data

No pooled analysis was planned for this review. Missing data regarding concomitant drug therapy were used to aid in describing the landscape of trials investigating MBIs for chronic pain patients with respect to drug therapy.

4. Results

4.1. Search results

The initial literature search identified 848 records with 1 additional citation identified through hand searching of other literature and clinical trial databases (**Fig. 1**). After excluding duplicates, there were 484 records. After initial screening of titles and abstracts, we identified 57 relevant records. After reading the full articles for these 57 studies, we excluded 17 studies (Supplemental Appendix 2, available at http://links.lww.com/PR9/A87). A total of 40 studies fulfilled the inclusion criteria and were included in our review.[2,5,6,10–12,14,16,20,23,24,26,27,30,31,35,39,41,44,50,52,56,59–62,64,65,67,70–72,75,78,79,81,82,85,86,90]

4.2. Included studies

The 40 included RCTs included a total of 2978 participants with chronic pain (**Tables 1 and 2**). The chronic pain conditions investigated varied and included unspecified or multiple chronic pain conditions,[10,24,26,30,31,52,67,78,85,86] fibromyalgia,[2,11,20,64,70,71,79,81] chronic low back pain,[6,16,27,44,59–61,90] chronic headache,[5,12,23,82] diabetic peripheral neuropathy,[62,75] chronic musculoskeletal pain,[65] postherpetic neuralgia,[56] HIV-associated chronic pain,[35] failed back surgery syndrome,[27] provoked localized vulvodynia,[39] spinal cord injury with chronic pain,[41] sickle cell disease with chronic pain,[72] bladder pain syndrome,[50] and medically unexplained pain.[14] Treatment periods ranged from a 10-minute body scan to, more commonly, 8 or more weeks of a structured mindfulness-based program. The most commonly used MBIs were mindfulness-based stress reduction (MBSR),[2,5,6,11,14,16,27,35,50,62,65,70,71,81,82,85,86] a variation of MBSR,[12,52,56,59–61,75] mindfulness-based cognitive therapy,[23,24,26,64] mindfulness-oriented recovery enhancement (MORE),[30,31] and others (mindfulness-based pain management program, mindfulness socioemotional regulation intervention, mindfulness-based group cognitive behaviour therapy, brief MBI, mindfulness awareness in body-oriented therapy, 6-week customized MBI, brief mindfulness-based body scan, second-generation MBI, and manualized meditation cognitive behavior therapy [CBT] intervention).[10,20,39,41,44,67,72,78,79,90]

4.3. Excluded studies

We excluded 17 studies after the full articles were reviewed.[4,15,21,22,28,29,32,37,38,42,45,46,74,83,84,89,91] Additional details regarding the reason(s) for exclusion can be found in Supplemental Appendix 2 (available at http://links.lww.com/PR9/A87).

4.4. Risk of bias

The results of each individual risk of bias domain are presented with a risk of bias graph shown in **Figure 2** and a risk of bias summary shown in **Figure 3**.

(1) Random sequence generation: All included studies were randomized, but only 26 of 40 adequately described the method that was used to generate the random sequence.
(2) Allocation concealment: 16 of 40 studies described how the sequence was concealed.
(3) Blinding of participants and personnel: Given the nature of MBIs, as with other psychological interventions, blinding of participants and personnel is difficult and thus contributed to a high risk of bias in all studies.

Table 1

Main characteristics of included trials of mindfulness for chronic pain.

Mindfulness intervention	First author, year	Chronic pain condition	No. of treatment arms	Comparator(s)	Treatment duration	Trial size
MBSR	Andres-Rodriguez,[2] 2019	Fibromyalgia	2	TAU	Weekly sessions for 8 weeks	MBSR, n = 35; TAU, n = 35
MBSR	Bakhshani,[5] 2015	Migraine, headache	2	TAU	Weekly sessions for 8 weeks	Total of 40 participants randomized into MBSR or comparator group; no details provided
MBSR	Banth,[6] 2015	Low back pain	2	TAU	Weekly sessions for 8 weeks	MBSR, n = 39; control, n = 48
MBSR	Cash,[11] 2015	Fibromyalgia	2	TAU	Weekly sessions for 8 weeks	MBSR, n = 51; control, n = 40
MBSR	Chavooshi,[14] 2016	Medically unexplained pain	3	ISTDP or TAU	Weekly sessions for 8 weeks	MBSR, n = 20; ISTDP, n = 23; TAU, n = 20
MBSR	Cherkin,[16] 2016	Back pain	3	CBT or TAU	Weekly sessions for 8 weeks	MBSR, n = 116; CBT, n = 113; TAU, n = 113
MBSR	Esmer,[27] 2010	Back pain, leg pain	2	TAU	Weekly sessions for 8 weeks	MBSR, n = 19; TAU, n = 21
MBSR	George,[35] 2017	HIV-associated chronic pain	2	Health education control	Weekly sessions for 8 weeks	MBSR, n = 16; control, n = 16
MBSR	Kanter,[50] 2016	Interstitial cystitis/bladder pain syndrome	2	TAU	Weekly sessions for 8 weeks	MBSR, n = 9; TAU, n = 11
MBSR	Nathan,[62] 2017	Painful diabetic peripheral neuropathy	2	TAU	Weekly sessions for 8 weeks	MBSR, n = 33; control, n = 33
MBSR	Plews-Ogan,[65] 2005	Musculoskeletal pain	3	Massage or TAU	Weekly sessions for 8 weeks	MBSR, n = 10; massage, n = 10; TAU, n = 10
MBSR	Schmidt,[70] 2011	Fibromyalgia	3	Relaxation intervention or TAU	Weekly sessions for 8 weeks	MBSR, n = 59; relax intervention, n = 59; control, n = 59
MBSR	Sephton,[71] 2007	Fibromyalgia	2	TAU	Weekly sessions for 8 weeks	MBSR, n = 51; control, n = 40
MBSR	Weissbecker,[81] 2002	Fibromyalgia	2	TAU	Weekly sessions for 8 weeks	MBSR, n = 51; control, n = 40
MBSR	Wells,[82] 2014	Migraines	2	TAU	Weekly sessions for 8 weeks	MBSR, n = 10; TAU, n = 9
MBSR	Wong,[85] 2009	Unspecified	2	Multidisciplinary education program	8 weeks	Not reported
MBSR	Wong,[86] 2011	Unspecified	2	Multidisciplinary pain intervention	Weekly sessions for 8 weeks	MBSR, n = 51; control, n = 49
MBSR variation	Cathcart,[12] 2014	Tension-type headache	2	TAU	Twice weekly sessions for 3 weeks	Treatment, n = 29; control, n = 29
MBSR variation	La Cour,[52] 2015	Varied	2	TAU	Weekly sessions for 8 weeks	Treatment, n = 54; control, n = 55
MBSR variation	Meize-Grochowski,[56] 2015	Postherpetic neuralgia	2	TAU	Daily mindfulness meditation for 6 weeks	Treatment, n = 16; TAU, n = 15
MBSR variation	Morone,[59] 2016	Low back pain	2	Health education program	Weekly sessions for 8 weeks	Treatment, n = 140; control, n = 142
MBSR variation	Morone,[61] 2009	Low back pain	2	Health education program	Weekly sessions for 8 weeks	Treatment, n = 20; control, n = 20
MBSR variation	Morone,[60] 2008	Low back pain	2	TAU	Weekly sessions for 8 weeks	Treatment, n = 19; control, n = 18
MBSR variation	Teixeira,[75] 2010	Diabetic peripheral neuropathy	2	Nutritional information and food diary	Listen to guided compact disc 5 days per week for 4 weeks	Treatment, n = 11; control, n = 11
MBCT	Day,[23] 2014	Headache	2	TAU	Weekly sessions for 8 weeks	MBCT, n = 19; control, n = 17
MBCT	De Jong,[24] 2018	Chronic pain with depression	2	TAU	Weekly session for 8 weeks	MBCT, n = 26; control, n = 14

(*continued on next page*)

Table 1 (*continued*)

Main characteristics of included trials of mindfulness for chronic pain.

Mindfulness intervention	First author, year	Chronic pain condition	No. of treatment arms	Comparator(s)	Treatment duration	Trial size
MBCT	Parra-Delagdo,[64] 2013	Fibromyalgia	2	TAU	8 group sessions over 3 months	MBCT, n = 17; TAU, n = 16
MBCT computerize	Dowd,[26] 2015	Chronic noncancer pain	2	Psychoeducation	Two online sessions per week for 6 weeks	MBCT, n = 62; control, n = 62
MORE	Garland,[31] 2014	Chronic noncancer pain	2	Support group	Weekly sessions for 8 weeks	MORE, n = 57; control, n = 58
MORE	Garland,[30] 2013	Chronic noncancer pain	2	Support group	Weekly sessions for 8 weeks	MORE, n = 50; control, n = 42
Manualized meditation-CBT intervention ("mindfulness for chronic pain")	Zgierska,[90] 2016	Low back pain	2	TAU and opioid therapy	Weekly sessions for 8 weeks	Treatment, n = 21; TAU and opioid therapy, n = 14
Mindfulness-based pain management program	Brown,[10] 2013	Fibromyalgia, rheumatoid arthritis, osteoarthritis, and other musculoskeletal pain	2	TAU	Weekly session for 8 weeks	Treatment, n = 20; TAU, n = 20
Mindfulness-based pain management (online intervention)	Hearn,[41] 2018	Spinal cord injury	2	Online psychoeducation	2 audio-guided meditations each day for 6 of 7 days a week, for 8 weeks	Treatment, n = 36; control, n = 31
Second-generation mindfulness-based intervention	Van Gordon,[79] 2017	Fibromyalgia	2	Cognitive behaviour theory for groups	Weekly sessions for 8 weeks	Treatment, n = 74; control, n = 74
Mindfulness-based group cognitive behaviour therapy	Guillet,[39] 2019	Provoked localized vulvodynia	2	Education support group	Weekly sessions for 8 weeks	Treatment, n = 14; control, n = 17
Brief mindfulness-based body scan	Ussher,[78] 2014	Unspecified	2	Reading about natural history	Single 10-minute mindfulness body scan	Treatment, n = 27; control, n = 28
Brief mindfulness-based intervention	Howarth,[44] 2019	Back pain and other	2	Distraction audios	Single 15-minute mindfulness body scan audio in the clinic, followed by independent use over 1 month	Treatment, n = 37; control, n = 34
6-Week customized mindfulness-based intervention	Simmons,[72] 2019	Sickle cell disease with chronic pain	2	TAU	Weekly telephonic sessions for 6 weeks	Treatment, n = 40; control, n = 20
Mindful socioemotional regulation intervention (Internet)	Davis,[20] 2013	Fibromyalgia	2	Healthy lifestyle tips (Internet)	Twelve modules to be completed over 6 weeks	Treatment, n = 39; control, n = 40
Mindfulness awareness in body-oriented therapy	Price,[67] 2007	Unspecified	2	TAU	Weekly sessions for 8 weeks	Treatment, n = 7; control, n = 7

CBT, cognitive behavioural therapy; ISTDP, intensive short-term dynamic psychotherapy; MBCT, mindfulness-based cognitive therapy; MBSR, mindfulness-based stress reduction; MORE, mindfulness-oriented recovery enhancement; TAU, treatment as usual.

(4) Blinding of outcome assessment: None of the studies adequately described how outcome assessment was blinded.
(5) Incomplete outcome data: Only 6 of 40 studies were judged at a low risk of bias for incomplete outcome assessment, which meant the remaining studies had greater than a 10% dropout rate and used last outcome carried forward imputation method or completer analysis.
(6) Selective reporting: 12 of 40 studies were judged to be at a low risk of bias for selective reporting, 26 of 40 studies at an unclear risk of bias, and only 2 of 40 studies at a high risk of bias.
(7) Other potential sources of bias: 0 of 40 studies contained over 200 participants per treatment arm and only 10 of 40 studies contained 50 to 199 participants per treatment arm. The remaining studies contained less than 50 participants per treatment arm.

4.5. Primary and secondary outcomes

The summary of findings is presented in **Tables 1 and 2**.

Only 1 of the 40 (2.5%) included trials prohibited participants to take CADTs during the trial. The one trial that explicitly did not allow CADTs investigated a MBSR variation for tension-type headaches.[12] This trial required participants to not be currently receiving, or have received in the past 12 months, intervention for their headache.

Only 6 of the 39 (15.4%) trials allowing CADTs provided adequate details on what CADTs participants were receiving,[2,16,60,65,78,86] such as what percentage of participants were receiving opioid and nonopioid treatments for their chronic pain. A trial by Andrés-Rodríguez et al.[2] that investigated MBSR for fibromyalgia reported that of 66 participants, 34.8% were taking NSAIDs, 12.1% were taking anticonvulsants, 36.4% were taking antidepressants, and

Table 2

Main results of this review's outcome measures.

Mindfulness intervention	First author, year	Chronic pain condition	Were concomitant pain treatments prohibited? (yes/no)	If concomitant pain treatments were described, what were they?	Did the trials control for concomitant pain treatments? (yes/no)	Did the trials analyze the interaction between the mindfulness-based intervention and the concomitant drug therapies? (yes/no)	Adverse events
MBSR	Andres-Rodriguez,[2] 2019	Fibromyalgia	No	Treatment group: 50.0% analgesics, 32.3% NSAIDs, 17.6% anticonvulsants, 44.1% antidepressants, 26.5% opioids, 2.9% muscle relaxants, and 32.4% anxiolytics. Control group: 37.5% analgesics, 37.5% NSAIDs, 6.3% anticonvulsants, 28.2% antidepressants, 9.4% opioids, 0.0% muscle relaxants, and 43.8% anxiolytics	No	No	Not reported
MBSR	Bakhshani,[5] 2015	Chronic headache	No	Not described	No	No	Not reported
MBSR	Banth,[6] 2015	Low back pain	No	Not described	No	No	Not reported
MBSR	Cash,[11] 2015	Fibromyalgia	No	Not described	No	No	Not reported
MBSR	Chavooshi,[14] 2016	Medically unexplained pain	No	Not described	No	No	Not reported
MBSR	Cherkin,[16] 2016	Back pain	No	11.1% reported using opioids for their pain in the past week; 73.9% reported using any medication for their pain in the past week	No	No	29% participants attending at least 1 MBSR session reported an adverse experience (mostly a temporary increase in pain with yoga)
MBSR	Esmer,[27] 2010	Back pain, leg pain	No	Not described	No	No	Not reported
MBSR	George,[35] 2017	HIV-associated chronic pain	No	Not described	No	No	Not reported
MBSR	Kanter,[50] 2016	Interstitial cystitis/bladder pain syndrome	No	Not described	No	No	Not reported
MBSR	Nathan,[62] 2017	Painful diabetic peripheral neuropathy	No	Not described	No	No	Not reported
MBSR	Plews-Ogan,[65] 2005	Musculoskeletal pain	No	All participants continued their use of prescribed pain medications. 60% were taking at least 1 narcotic medication, and 40% were taking only non-narcotic medications.	No	No	Not reported
MBSR	Schmidt,[70] 2011	Fibromyalgia	No	Not described	No	No	Not reported
MBSR		Fibromyalgia	No		No	No	Not reported

(*continued on next page*)

Table 2 (*continued*)

Main results of this review's outcome measures.

Mindfulness intervention	First author, year	Chronic pain condition	Were concomitant pain treatments prohibited? (yes/no)	If concomitant pain treatments were described, what were they?	Did the trials control for concomitant pain treatments? (yes/no)	Did the trials analyze the interaction between the mindfulness-based intervention and the concomitant drug therapies? (yes/no)	Adverse events
	Sephton,[71] 2007			Incompletely described Medications reported among the sample included antidepressants (63.7%), anxiolytics (23.1%), and hypnotics (9.9%)			
MBSR	Weissbecker,[81] 2002	Fibromyalgia	No	Not described	No	No	Not reported
MBSR	Wells,[82] 2014	Migraines	No	Incompletely described 80% of the treatment group and 89% of the control group were taking daily prophylactic medications. All participants were taking abortive headache medications.	No	No	No adverse events occurred among participants
MBSR	Wong,[85] 2009	Unspecified	No	Not described	No	No	Not reported
MBSR	Wong,[86] 2011	Unspecified	No	Treatment group: 64.7% acetaminophen, 29.4% rheumatic pain killer, 2.0% opioids, and 17.6% no analgesic use. Control group: 64.5% acetaminophen, 31.3% rheumatic pain killer, 0% opioids, and 12.5% no analgesic use.	No	No	Not reported
MBSR variation	Cathcart,[12] 2014	Tension-type headache	Yes	N/a	N/a	N/a	Not reported
MBSR variation	La Cour,[52] 2015	Varied	No	Incompletely described Opioid use in years, mean (SD): 4.13 (4.32) in the treatment group and 5.69 (5.88) in the control group	No	No	At least 2 participants experienced transient strong feelings of anger toward their pain condition and at least 2 participants experienced greater anxiety
MBSR variation	Meize-Grochowski,[56] 2015	Postherpetic neuralgia	No	Not described	No	No	Not reported
MBSR variation	Morone,[59] 2016	Low back pain	No	Not described	No	No	No adverse events occurred among participants

(*continued on next page*)

Table 2 (*continued*)

Main results of this review's outcome measures.

Mindfulness intervention	First author, year	Chronic pain condition	Were concomitant pain treatments prohibited? (yes/no)	If concomitant pain treatments were described, what were they?	Did the trials control for concomitant pain treatments? (yes/no)	Did the trials analyze the interaction between the mindfulness-based intervention and the concomitant drug therapies? (yes/no)	Adverse events
MBSR variation	Morone,[61] 2009	Low back pain	No	Not described	No	No	No adverse events occurred among participants
MBSR variation	Morone,[60] 2008	Low back pain	No	Treatment group: 21.1% opioids, 68.4% other analgesics, and 10.5% none Control group: 16.7% opioids, 66.7% other analgesics, and 16.7% none	No	No	No adverse events occurred among participants
MBSR variation	Teixeira,[75] 2010	Diabetic peripheral neuropathy	No	Incompletely described Extrastrength acetaminophen was reported as the most frequently used over-the-counter pain reliever. Most reported pain medications included narcotics, antidepressants, pregabalin, and gabapentin (numbers not provided). 20% of participants reported using complementary therapies to treat their painful symptoms (eg, chiropractics).	No	No	Reported side effects experienced included dizziness, unsteadiness, and inability to think clearly
MBCT	Day,[23] 2014	Headache	No	Not described	No	No	Not reported
MBCT	De Jong,[24] 2018	Chronic pain with depression	No	Not described	No	No	One participant experienced spiritual issues, possibly related to the intervention
MBCT	Parra-Delgado,[64] 2013	Fibromyalgia	No	Incompletely described Treatment group: 33.3% antidepressants Control group: 43.7% antidepressants	No	No	Not reported

(*continued on next page*)

Table 2 (*continued*)

Main results of this review's outcome measures.

Mindfulness intervention	First author, year	Chronic pain condition	Were concomitant pain treatments prohibited? (yes/no)	If concomitant pain treatments were described, what were they?	Did the trials control for concomitant pain treatments? (yes/no)	Did the trials analyze the interaction between the mindfulness-based intervention and the concomitant drug therapies? (yes/no)	Adverse events
MBCT computerize	Dowd,[26] 2015	Chronic noncancer pain	No	Incompletely described Previous treatments in the treatment group: 51.6% medication only, 38.7% medications + other treatments, 1.6% yoga, 1.6% meditation, and 3.2% psychological Previous treatments in the control group: 58.1% medication only, 38.7% medications + other treatments, and 1.6% psychological	No	No	Not reported
MORE	Garland,[31] 2014	Chronic noncancer pain	No	Incompletely described Inclusion criteria required participants to have been prescribed and taken opioids for analgesia daily or nearly every day for at least the past 90 days	Yes Both groups required patients to be prescribed and have taken opioids for their pain	No	Not reported
MORE	Garland,[30] 2013	Chronic noncancer pain	No	Incompletely described Inclusion criteria required participants to have been prescribed and taken opioids for analgesia daily or nearly every day for at least the past 90 days	Yes Both groups required patients to be prescribed and have taken opioids for their pain	No	Not reported
Manualized meditation-CBT intervention, usual care, and opioid therapy	Zgierska,[90] 2016	Low back pain	No	Incompletely described Participants were treated with opioid therapy for 7.9 ± 5.7 years.	Yes To be eligible, participants had to have been treated by a clinician with daily opioid therapy (at least 30 mg/d of morphine-related dose) for at least 3 months.	No	Only anticipated, mild, and self-limited mild side effects were reported by the participants
Mindfulness-based pain management program	Brown,[10] 2013	Fibromyalgia, rheumatoid arthritis, osteoarthritis, and other musculoskeletal pain	No	Not described	No	No	Not reported

(*continued on next page*)

Table 2 (*continued*)

Main results of this review's outcome measures.

Mindfulness intervention	First author, year	Chronic pain condition	Were concomitant pain treatments prohibited? (yes/no)	If concomitant pain treatments were described, what were they?	Did the trials control for concomitant pain treatments? (yes/no)	Did the trials analyze the interaction between the mindfulness-based intervention and the concomitant drug therapies? (yes/no)	Adverse events
Mindfulness-based pain management (online intervention)	Hearn,[41] 2018	Spinal cord injury	No	Not described	No	No	Not reported
Second-generation mindfulness-based intervention	Van Gordon,[79] 2017	Fibromyalgia	No	Not described	No	No	Not reported
Mindfulness-based group cognitive behaviour therapy	Guillet,[39] 2019	Provoked localized vulvodynia	No	Not described	No	No	Not reported
Brief mindfulness-based body scan	Ussher,[78] 2014	Unspecified	No	Treatment group: 55.6% opioids, 63.0% nonopioid analgesia, and 48.1% neuropathic analgesia Control group: 39.3% opioids, 71.4% nonopioid analgesia, and 28.6% neuropathic analgesia	No	No	Not reported
Brief mindfulness-based intervention	Howarth,[44] 2019	Back pain and others	No	Not described	No	No	Not reported
6-Week customized mindfulness-based intervention	Simmons,[72] 2019	Sickle cell disease with chronic pain	No	Not described	No	No	Not reported
Mindful socioemotional regulation intervention (Internet)	Davis,[20] 2013	Fibromyalgia	No	Not described	No	No	Not reported
Mindfulness awareness in body-oriented therapy	Price,[67] 2007	Unspecified	No	Not described	Yes Participants must have been taking analgesics for their chronic pain to be enrolled.	No	Not reported

CBT, cognitive behavioural therapy; MBCT, mindfulness-based cognitive therapy; MBSR, mindfulness-based stress reduction; MORE, mindfulness-oriented recovery enhancement; NSAIDs, nonsteroidal anti-inflammatory drugs.

18.2% were taking opioids. A trial by Cherkin et al.[16] that investigated MBSR for low back pain reported that of 341 participants, 11.1% of participants were taking opioids and 73.9% were taking any medication for their low back pain. A trial by Plews-Ogan et al.[65] that investigated MBSR for musculoskeletal pain reported that of 30 participants, 60% were taking at least 1 narcotic medication and 40% were taking only non-narcotic medications. A trial by Wong et al.[86] that investigated MBSR for chronic pain that was unspecified reported that of 100 participants, 64% were taking acetaminophen, 30% were taking a rheumatic pain killer, 1% were taking opioids, and 15% were taking no analgesics. A trial by Morone et al.[60] that investigated a MBSR variation for low back pain reported that of 37

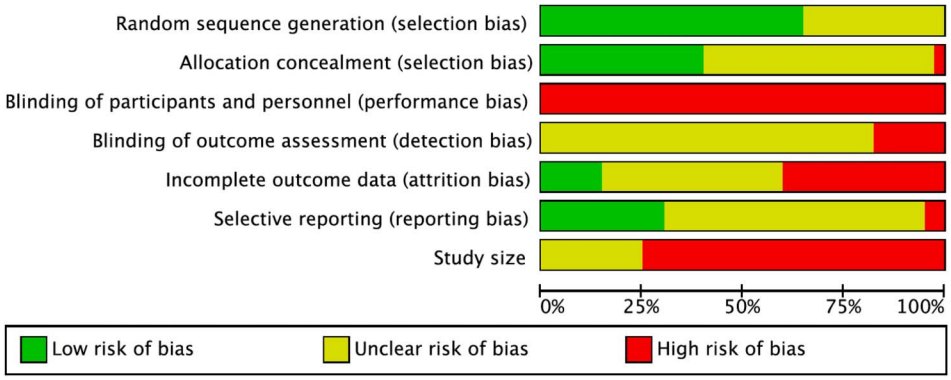

Figure 2. Risk of bias graph: Review the authors' judgement about each risk of bias item presented as percentages across all included studies.

participants, 18.9% were taking opioids, 70.3% were taking other analgesics, and 13.5% were taking no medications for their low back pain. Finally, a trial by Ussher et al.[78] that investigated a brief mindfulness-based body scan for chronic pain that was unspecified reported that of 55 participants, 47.3% were taking opioids, 67.3% were taking nonopioid medications, and 38.2% were taking neuropathic analgesics. Otherwise, 9 of 39 (23.1%) trials provided incomplete details on what CADTs trial participants were receiving, and the remaining trials provided no details. Additional details can be found on **Table 2**.

Of the 39 trials that allowed CADTs, only 4 (10.3%) trials had specific medication requirements for entry.[30,31,67,90] Two of these trials by Garland et al.,[30,31] which investigated MORE for chronic noncancer pain, required all participants to have had used prescription opioids for analgesia every day or nearly every day for at least 90 days. A trial by Zgierska et al.[90] that investigated mindfulness meditation with CBT for low back pain required participants to have had been treated by a clinician with daily opioid therapy (at least 30 mg/d of morphine-equivalent dose) for at least 3 months. Finally, a trial by Price et al.[67] that investigated mindfulness awareness in body-oriented therapy for chronic pain that was unspecified required participants to be using prescription analgesics.

Of great relevance to this review, none of the 39 trials that allowed for CADTs analyzed the interaction between MBIs and the CADTs to determine whether they have additive analgesic benefit. Because the interaction was not analyzed, the review's secondary outcome of how MBIs plus CADTs differed from only drug therapy in managing secondary features of chronic pain (ie, depression, physical and mental health-related quality of life, and functional disability) could not be reported.

4.6. Adverse events

The adverse events experienced by participants between those who received MBI compared with those who received another control treatment were inconsistently reported, and no meaningful statistical analyses could be performed. Only 9 of 40 (22.5%) trials reported any information on adverse events. Four reported no adverse events occurred[59–61,82]; one stated only mild and self-limited mild side effects were reported[90]; one stated that at least 2 participants experienced transient strong feelings of anger toward their pain condition and at least 2 participants experienced greater anxiety[52]; one reported no serious adverse events but reported that 30 of 103 (29%) participants attending at least 1 MBSR session reported an adverse event (mostly a temporary increase in pain with yoga)[16]; one reported no significant adverse events except one participant in the mindfulness-based cognitive therapy group who had spiritual issues possibly related to the treatment[24]; and one reported side effects of dizziness, unsteadiness, and inability to think clearly.[75]

5. Discussion

This systematic scoping review evaluated the current state of mindfulness-based clinical trials for chronic pain with respect to CADTs, attempted to evaluate available evidence on interaction effects between MBIs and various drug treatments, and assessed harms of MBIs. We found that only one of 40 (2.5%) included trials forbid participants from taking CADTs during the trial, meaning that participants in the remaining 39 (97.5%) trials were permitted to take, and were likely taking, CADTs.[7] However, our review found that only 15.4% of trials provided sufficient details on what CADTs participants were taking and only 10.3% of trials had specific medication requirements for entry. Of great relevance to this review, none of the included trials analyzed the interactions between MBIs and the CADTs the participants were taking to determine whether they had an antagonistic, additive, or even multiplicative effect.

It is recognized that it was not the intention or aim of the authors undertaking the included RCTs to analyze the interaction between MBIs and CADTs. To better quantify the individual effects of MBIs, future studies should collect and report what CADTs participants were taking. Precise details of these interventions and how and when they were actually administered should be reported. It would also be beneficial if attempts are made to ensure that CADTs are equivalent between groups (eg, stratified randomization). Trials could also have specific medication requirements for entry (eg, patients required to be taking a specific opioid) or exclude participants taking specific medications. Precise details of the eligibility criteria should be reported. Although this does not guarantee that the groups are equivalent, the results can be interpreted with greater confidence.

The emerging evidence supporting the safe use of MBIs for chronic pain, well-established efficacy and safety of many analgesic drugs, and assumption that MBIs and analgesic drugs manage pain by different mechanisms suggests that MBIs may be complementary to pharmacotherapy. Ideally, combination therapies should have different pain-reducing mechanisms or site of actions. Mechanistically, pharmacotherapy can target a variety of peripheral, spinal, and supraspinal sites (depending on the drug) to reduce pain, whereas MBIs likely act through different mechanisms. Although our understanding of the physiological

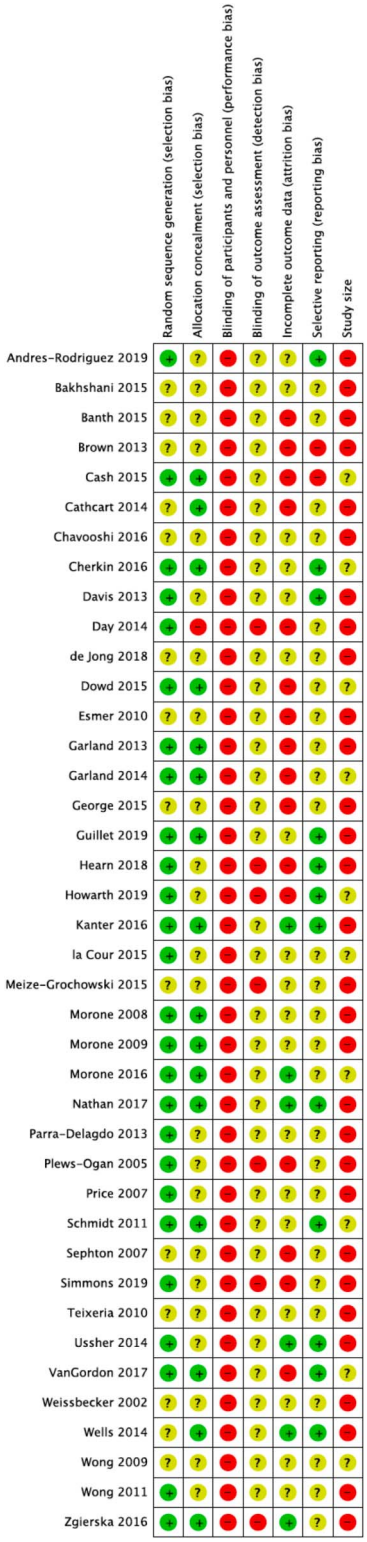

Figure 3. Risk of bias summary: Review the authors' judgements about each risk of bias item for each included study.

impacts of MBIs on the brain is in its early stages, recent functional magnetic resonance imaging studies demonstrate neural mechanisms supporting mindfulness-based pain reduction. As an example, pain reduction after prolonged mindfulness-based practice (greater than 1000 hours) was associated with deactivation of prefrontal and greater activation of somatosensory cortical regions, showing its ability to attenuate reactions of arising sensory events.[40,87] Mindfulness-based interventions have also been shown to moderate the relationship between pain intensity and pain catastrophizing.[66] In addition, treatments should have nonoverlapping side effects, which is also the case for MBIs and most pharmacotherapies. This is especially important in light of the opioid crisis and given the dose-limiting adverse effects of many drug treatments. Thus, their rational combination for chronic pain should be studied, especially because less than a third of patients report at least moderate pain relief with a single agent.[36]

The rational combination of psychotherapy and pharmacotherapy has been studied in many other medical contexts. A meta-analysis by Cuijpers et al.[19] found that combining psychotherapy with antidepressant medications was more effective than treatment with antidepressants alone for major depression, panic disorder, and obsessive-compulsive disorder. Another meta-analysis by Kamenov et al.[49] also found that the combination of psychotherapy and pharmacotherapy performed better than either alone in improving functioning and quality of life in patients with depression. The combination of pharmacotherapy and psychosocial interventions has also been found to be more beneficial than monotherapy in treating smoking cessation (eg, combination of bupropion with psychological support) and alcohol dependence (eg, naltrexone or acamprosate combined with CBT).[25,69,73,80] Studies have also suggested that psychotherapy combined with pharmacotherapy was more acceptable to patients than pharmacotherapy alone.[18] These findings are likely, at least in part, attributable to the principle that targeting 2 different mechanisms is more effective than one. In theory, the same rationale can be applied to combination therapy for chronic pain. Thus, comparable attention is now needed for the combination of analgesic drugs with MBIs and other similar interventions in chronic pain.

A major limitation of this review must be acknowledged. The purpose of our review was to summarize the landscape of mindfulness-based trials with respect to drug therapy. Thus, to provide a discrete set of results, we only focused on a subset of mindfulness interventions. However, despite us selectively excluding potentially relevant trials, our findings still emphasize the need for further research in this area.

6. Conclusion

In conclusion, this systematic scoping review suggests that, currently, mindfulness-based trials for chronic pain rarely describe what CADTs the participants were receiving and rarely control for these CADTs. Notably, we found that none of the included trials analyzed interaction effects between MBIs and CADTs for chronic pain. No judgments could be made about safety because adverse events were inconsistently reported. To better understand how MBIs can and should be integrated into patients' multidisciplinary pain management, large clinical trials that analyze the interaction between MBIs and CADTs are needed. Better harms assessment and reporting are also needed in mindfulness-based chronic pain trials.

Disclosures

The authors have no conflicts of interest to declare.

Acknowledgements

The authors thank Sandra Halliday for her assistance in building the search strategy.

This work was supported, in part, by the Queen's University Department of Anesthesiology & Perioperative Medicine and the Chronic Pain Network of the Canadian Institutes of Health Research Strategy on Patient-Oriented Research.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A87.

Article history:
Received 15 June 2020
Received in revised form 29 August 2020
Accepted 22 September 2020

References

[1] Alford DP. Opioid prescribing for chronic pain—achieving the right balance through education. N Engl J Med 2016;374:301–3.
[2] Andrés-Rodríguez L, Borràs X, Feliu-Soler A, Pérez-Aranda A, Rozadilla-Sacanell A, Montero-Marin J, Maes M, Luciano JV. Immune-inflammatory pathways and clinical changes in fibromyalgia patients treated with Mindfulness-Based Stress Reduction (MBSR): a randomized, controlled clinical trial. Brain Behav Immun 2019;80:109–19.
[3] Andrew R, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. Pain Pract 2014;14:79–94.
[4] Astin JA, Berman BM, Bausell B, Lee WL, Hochberg M, Forys KL. The efficacy of mindfulness meditation plus Qigong movement therapy in the treatment of fibromyalgia: a randomized controlled trial. J Rheumatol 2003;30:2257–62.
[5] Bakhshani NM, Amirani A, Amirifard H, Shahrakipoor M. The effectiveness of mindfulness-based stress reduction on perceived pain intensity and quality of life in patients with chronic headache. Glob J Health Sci 2015;8:142–51.
[6] Banth S, Ardebil MD. Effectiveness of mindfulness meditation on pain and quality of life of patients with chronic low back pain. Int J Yoga 2015;8:128–33.
[7] Berger A, Sadosky A, Dukes E, Edelsberg J, Oster G. Clinical characteristics and patterns of healthcare utilization in patients with painful neuropathic disorders in UK general practice: a retrospective cohort study. BMC Neurol 2012;12:8.
[8] Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, Segal ZV, Abbey S, Speca M, Velting D. Mindfulness: a proposed operational definition. Clin Psychol Sci Pract 2004;11:230–41.
[9] Borsook D. A future without chronic pain: neuroscience and clinical research. Cerebrum 2012;2012:7.
[10] Brown CA, Jones AK. Psychobiological correlates of improved mental health in patients with musculoskeletal pain after a mindfulness-based pain management program. Clin J Pain 2013;29:233–44.
[11] Cash E, Salmon P, Weissbecker I, Rebholz WN, Bayley-Veloso R, Zimmaro LA, Floyd A, Dedert E, Sephton SE. Mindfulness meditation alleviates fibromyalgia symptoms in women: results of a randomized clinical trial. Ann Behav Med 2015;49:319–30.
[12] Cathcart S, Galatis N, Immink M, Proeve M, Petkov J. Brief mindfulness-based therapy for chronic tension-type headache: a randomized controlled pilot study. Behav Cogn Psychother 2014;42:1–15.
[13] Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. PAIN 2004;109:514–19.
[14] Chavooshi B, Mohammadkhani P, Dolatshahee B. Efficacy of intensive short-term dynamic psychotherapy for medically unexplained pain: a pilot three-armed randomized controlled trial comparison with mindfulness-based stress reduction. Psychother Psychosom 2016;85:123–5.
[15] Cherkin DC, Anderson ML, Sherman KJ, Balderson BH, Cook AJ, Hansen KE, Turner JA. Two-year follow-up of a randomized clinical trial of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care for chronic low back pain. JAMA 2017;317:642–4.
[16] Cherkin DC, Sherman KJ, Balderson BH, Cook AJ, Anderson ML, Hawkes RJ, Hansen KE, Turner JA. Effect of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain and functional limitations in adults with chronic low back pain: a randomized clinical trial. JAMA 2016;315:1240–9.
[17] Cherry DK, Woodwell DA, Rechtsteiner EA. National ambulatory medical care survey: 2005 summary. Adv Data 2007:1–39.
[18] Cuijpers P, Noma H, Karyotaki E, Vinkers CH, Cipriani A, Furukawa TA. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry 2020;19:92–107.
[19] Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF III. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. World Psychiatry 2014;13:56–67.
[20] Davis MC, Zautra AJ. An online mindfulness intervention targeting socioemotional regulation in fibromyalgia: results of a randomized controlled trial. Ann Behav Med 2013;46:273–84.
[21] Davis MC, Zautra AJ, Wolf LD, Tennen H, Yeung EW. Mindfulness and cognitive-behavioral interventions for chronic pain: differential effects on daily pain reactivity and stress reactivity. J Consult Clin Psychol 2015;83:24–35.
[22] Day MA, Thorn BE. Mindfulness-based cognitive therapy for headache pain: an evaluation of the long-term maintenance of effects. Complement Ther Med 2017;33:94–8.
[23] Day MA, Thorn BE, Ward LC, Rubin N, Hickman SD, Scogin F, Kilgo GR. Mindfulness-based cognitive therapy for the treatment of headache pain: a pilot study. Clin J Pain 2014;30:152–61.
[24] de Jong M, Peeters F, Gard T, Ashih H, Doorley J, Walker R, Rhoades L, Kulich RJ, Kueppenbender KD, Alpert JE, Hoge EA, Britton WB, Lazar SW, Fava M, Mischoulon D. A randomized controlled pilot study on mindfulness-based cognitive therapy for unipolar depression in patients with chronic pain. J Clin Psychiatry 2018;79:15m10160.
[25] De Sousa A. The pharmacotherapy of alcohol dependence: a state of the art review. Mens Sana Monogr 2010;8:69–82.
[26] Dowd H, Hogan MJ, McGuire BE, Davis MC, Sarma KM, Fish RA, Zautra AJ. Comparison of an online mindfulness-based cognitive therapy intervention with online pain management psychoeducation: a randomized controlled study. Clin J Pain 2015;31:517–27.
[27] Esmer G, Blum J, Rulf J, Pier J. Mindfulness-based stress reduction for failed back surgery syndrome: a randomized controlled trial. J Am Osteopath Assoc 2010;110:646–52.
[28] Feuille M, Pargament K. Pain, mindfulness, and spirituality: a randomized controlled trial comparing effects of mindfulness and relaxation on pain-related outcomes in migraineurs. J Health Psychol 2015;20:1090–106.
[29] Garland EL, Bryan CJ, Finan PH, Thomas EA, Priddy SE, Riquino MR, Howard MO. Pain, hedonic regulation, and opioid misuse: modulation of momentary experience by Mindfulness-Oriented Recovery Enhancement in opioid-treated chronic pain patients. Drug Alcohol Depend 2017;173(suppl 1):S65–s72.
[30] Garland EL, Howard MO. Mindfulness-oriented recovery enhancement reduces pain attentional bias in chronic pain patients. Psychother Psychosom 2013;82:311–18.
[31] Garland EL, Manusov EG, Froeliger B, Kelly A, Williams JM, Howard MO. Mindfulness-oriented recovery enhancement for chronic pain and prescription opioid misuse: results from an early-stage randomized controlled trial. J Consult Clin Psychol 2014;82:448–59.
[32] Garland EL, Thomas E, Howard MO. Mindfulness-oriented recovery enhancement ameliorates the impact of pain on self-reported psychological and physical function among opioid-using chronic pain patients. J Pain Symptom Manage 2014;48:1091–9.
[33] Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain 2012;13:715–24.
[34] Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull 2007;133:581–624.
[35] George MC, Wongmek A, Kaku M, Nmashie A, Robinson-Papp J. A mixed-methods pilot study of mindfulness-based stress reduction for HIV-associated chronic pain. Behav Med 2017;43:108–19.
[36] Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol 2013;12:1084–95.
[37] Grossman P, Deuring G, Walach H, Schwarzer B, Schmidt S. Mindfulness-based intervention does not influence cardiac autonomic control or the pattern of physical activity in fibromyalgia during daily life: an ambulatory, multimeasure randomized controlled trial. Clin J Pain 2017;33:385–94.
[38] Grossman P, Tiefenthaler-Gilmer U, Raysz A, Kesper U. Mindfulness training as an intervention for fibromyalgia: evidence of postintervention and 3-year follow-up benefits in well-being. Psychother Psychosom 2007;76:226–33.
[39] Guillet AD, Cirino NH, Hart KD, Leclair CM. Mindfulness-based group cognitive behavior therapy for provoked localized vulvodynia: a randomized controlled trial. J Low Genit Tract Dis 2019;23:170–5.

[40] Hatchard T, Mioduszewski O, Zambrana A, O'Farrell E, Caluyong M, Poulin PA, Smith AM. Neural changes associated with mindfulness-based stress reduction (MBSR): current knowledge, limitations, and future directions. Psychol Neurosci 2017;10:41.
[41] Hearn JH, Finlay KA. Internet-delivered mindfulness for people with depression and chronic pain following spinal cord injury: a randomized, controlled feasibility trial. Spinal Cord 2018;56:750–61.
[42] Heffner K, Talbot N, Krasner M, Moynihan J. 93. Pain in older men is associated with interleukin (IL)-6 change across time following a mindfulness-based stress reduction intervention. Brain Behav Immun 2011;25:S205.
[43] Hilton L, Hempel S, Ewing BA, Apaydin E, Xenakis L, Newberry S, Colaiaco B, Maher AR, Shanman RM, Sorbero ME, Maglione MA. Mindfulness meditation for chronic pain: systematic review and meta-analysis. Ann Behav Med 2017;51:199–213.
[44] Howarth A, Riaz M, Perkins-Porras L, Smith JG, Subramaniam J, Copland C, Hurley M, Beith I, Ussher M. Pilot randomised controlled trial of a brief mindfulness-based intervention for those with persistent pain. J Behav Med 2019;42:999–1014.
[45] Jay K, Brandt M, Jakobsen MD, Sundstrup E, Berthelsen KG, Schraefel M, Sjøgaard G, Andersen LL. Ten weeks of physical-cognitive-mindfulness training reduces fear-avoidance beliefs about work-related activity: randomized controlled trial. Medicine (Baltimore) 2016;95:e3945.
[46] Johannsen M, O'Connor M, O'Toole MS, Jensen AB, Højris I, Zachariae R. Efficacy of mindfulness-based cognitive therapy on late post-treatment pain in women treated for primary breast cancer: a randomized controlled trial. J Clin Oncol 2016;34:3390–9.
[47] Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. Gen Hosp Psychiatry 1982;4: 33–47.
[48] Kaiser U, Treede RD, Sabatowski R. Multimodal pain therapy in chronic noncancer pain-gold standard or need for further clarification? PAIN 2017;158:1853–9.
[49] Kamenov K, Twomey C, Cabello M, Prina AM, Ayuso-Mateos JL. The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: a meta-analysis. Psychol Med 2017;47:414–25.
[50] Kanter G, Komesu YM, Qaedan F, Jeppson PC, Dunivan GC, Cichowski SB, Rogers RG. Mindfulness-based stress reduction as a novel treatment for interstitial cystitis/bladder pain syndrome: a randomized controlled trial. Int Urogynecol J 2016;27:1705–11.
[51] Kerns RD, Krebs EE, Atkins D. Making integrated multimodal pain care a reality: A path forward. J Gen Intern Med 2018;33(Suppl 1):1–3.
[52] la Cour P, Petersen M. Effects of mindfulness meditation on chronic pain: a randomized controlled trial. Pain Med 2015;16:641–52.
[53] Lynch ME. The need for a Canadian pain strategy. Pain Res Manag 2011; 16:77–80.
[54] Lynch ME, Watson CP. The pharmacotherapy of chronic pain: a review. Pain Res Manag 2006;11:11–38.
[55] Majeed MH, Ali AA, Sudak DM. Mindfulness-based interventions for chronic pain: evidence and applications. Asian J Psychiatr 2018;32: 79–83.
[56] Meize-Grochowski R, Shuster G, Boursaw B, DuVal M, Murray-Krezan C, Schrader R, Smith BW, Herman CJ, Prasad A. Mindfulness meditation in older adults with postherpetic neuralgia: a randomized controlled pilot study. Geriatr Nurs 2015;36:154–60.
[57] Miaskowski C, Blyth F, Nicosia F, Haan M, Keefe F, Smith A, Ritchie C. A biopsychosocial model of chronic pain for older adults. Pain Med 2019; 21:1793–805.
[58] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.
[59] Morone NE, Greco CM, Moore CG, Rollman BL, Lane B, Morrow LA, Glynn NW, Weiner DK. A mind-body program for older adults with chronic low back pain: a randomized clinical trial. JAMA Intern Med 2016;176: 329–37.
[60] Morone NE, Greco CM, Weiner DK. Mindfulness meditation for the treatment of chronic low back pain in older adults: a randomized controlled pilot study. PAIN 2008;134:310–19.
[61] Morone NE, Rollman BL, Moore CG, Li Q, Weiner DK. A mind-body program for older adults with chronic low back pain: results of a pilot study. Pain Med 2009;10:1395–407.
[62] Nathan HJ, Poulin P, Wozny D, Taljaard M, Smyth C, Gilron I, Sorisky A, Lochnan H, Shergill Y. Randomized trial of the effect of mindfulness-based stress reduction on pain-related disability, pain intensity, health-related quality of life, and A1C in patients with painful diabetic peripheral neuropathy. Clin Diabetes 2017;35:294–304.
[63] Park R, Mohiuddin M, Poulin P, Salomons T, Edwards R, Nathan H, Haley C, Gilron I. Interactions between analgesic drug therapy and mindfulness-based interventions for chronic pain in adults: protocol for a systematic scoping review. Pain Rep 2019;4:e793.
[64] Parra-Delgado M, Latorre-Postigo JM. Effectiveness of mindfulness-based cognitive therapy in the treatment of fibromyalgia: a randomised trial. Cogn Ther Res 2013;37:1015–26.
[65] Plews-Ogan M, Owens JE, Goodman M, Wolfe P, Schorling J. A pilot study evaluating mindfulness-based stress reduction and massage for the management of chronic pain. J Gen Intern Med 2005;20:1136–8.
[66] Poulin PA, Romanow HC, Rahbari N, Small R, Smyth CE, Hatchard T, Solomon BK, Song X, Harris CA, Kowal J, Nathan HJ, Wilson KG. The relationship between mindfulness, pain intensity, pain catastrophizing, depression, and quality of life among cancer survivors living with chronic neuropathic pain. Support Care Cancer 2016;24:4167–75.
[67] Price CJ, McBride B, Hyerle L, Kivlahan DR. Mindful awareness in body-oriented therapy for female veterans with post-traumatic stress disorder taking prescription analgesics for chronic pain: a feasibility study. Altern Ther Health Med 2007;13:32–40.
[68] Reiner K, Tibi L, Lipsitz JD. Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. Pain Med 2013;14: 230–42.
[69] Rovina N, Nikoloutsou I, Katsani G, Dima E, Fransis K, Roussos C, Gratziou C. Effectiveness of pharmacotherapy and behavioral interventions for smoking cessation in actual clinical practice. Ther Adv Respir Dis 2009;3:279–87.
[70] Schmidt S, Grossman P, Schwarzer B, Jena S, Naumann J, Walach H. Treating fibromyalgia with mindfulness-based stress reduction: results from a 3-armed randomized controlled trial. PAIN 2011;152:361–9.
[71] Sephton SE, Salmon P, Weissbecker I, Ulmer C, Floyd A, Hoover K, Studts JL. Mindfulness meditation alleviates depressive symptoms in women with fibromyalgia: results of a randomized clinical trial. Arthritis Rheum 2007;57:77–85.
[72] Simmons LA, Williams H, Silva S, Keefe F, Tanabe P. Acceptability and feasibility of a mindfulness-based intervention for pain catastrophizing among persons with sickle cell disease. Pain Manag Nurs 2019;20: 261–9.
[73] Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2016:CD008286.
[74] Steurer J. Mindfulness-based stress reduction is effective in patients with chronic lumbar backache [in German]. Praxis (Bern 1994) 2016;105: 721–2.
[75] Teixeira E. The effect of mindfulness meditation on painful diabetic peripheral neuropathy in adults older than 50 years. Holist Nurs Pract 2010;24:277–83.
[76] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). PAIN 2019;160:19–27.
[77] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JW, Wang SJ. A classification of chronic pain for ICD-11. PAIN 2015;156:1003–7.
[78] Ussher M, Spatz A, Copland C, Nicolaou A, Cargill A, Amini-Tabrizi N, McCracken LM. Immediate effects of a brief mindfulness-based body scan on patients with chronic pain. J Behav Med 2014;37:127–34.
[79] Van Gordon W, Shonin E, Dunn TJ, Garcia-Campayo J, Griffiths MD. Meditation awareness training for the treatment of fibromyalgia syndrome: a randomized controlled trial. Br J Health Psychol 2017;22: 186–206.
[80] Weiss RD, Kueppenbender KD. Combining psychosocial treatment with pharmacotherapy for alcohol dependence. J Clin Psychopharmacol 2006;26(suppl 1):S37–42.
[81] Weissbecker I, Salmon P, Studts JL, Floyd AR, Dedert EA, Sephton SE. Mindfulness-based stress reduction and sense of coherence among women with fibromyalgia. J Clin Psychol Med Settings 2002;9:297–307.
[82] Wells RE, Burch R, Paulsen RH, Wayne PM, Houle TT, Loder E. Meditation for migraines: a pilot randomized controlled trial. Headache 2014;54:1484–95.
[83] Westenberg RF, Zale EL, Heinhuis TJ, Özkan S, Nazzal A, Lee S-G, Chen NC, Vranceanu AM. Does a brief mindfulness exercise improve outcomes in upper extremity patients? A randomized controlled trial. Clin Orthop Relat Res 2018;476:790.

[84] Wetherell JL, Petkus AJ, Alonso-Fernandez M, Bower ES, Steiner AR, Afari N. Age moderates response to acceptance and commitment therapy vs. cognitive behavioral therapy for chronic pain. Int J Geriatr Psychiatry 2016;31:302–8.
[85] Wong SY. Effect of mindfulness-based stress reduction programme on pain and quality of life in chronic pain patients: a randomised controlled clinical trial. Hong Kong Med J 2009;15(suppl 6):13–14.
[86] Wong SY, Chan FW, Wong RL, Chu MC, Kitty Lam YY, Mercer SW, Ma SH. Comparing the effectiveness of mindfulness-based stress reduction and multidisciplinary intervention programs for chronic pain: a randomized comparative trial. Clin J Pain 2011;27:724–34.
[87] Zeidan F, Baumgartner JN, Coghill RC. The neural mechanisms of mindfulness-based pain relief: a functional magnetic resonance imaging-based review and primer. Pain Rep 2019;4:e759.
[88] Zeidan F, Grant JA, Brown CA, McHaffie JG, Coghill RC. Mindfulness meditation-related pain relief: evidence for unique brain mechanisms in the regulation of pain. Neurosci Lett 2012;520:165–73.
[89] Zgierska AE, Burzinski CA, Cox J, Kloke J, Singles J, Mirgain S, Stegner A, Cook DB, Bačkonja M. Mindfulness meditation-based intervention is feasible, acceptable, and safe for chronic low back pain requiring long-term daily opioid therapy. J Altern Complement Med 2016;22:610–20.
[90] Zgierska AE, Burzinski CA, Cox J, Kloke J, Stegner A, Cook DB, Singles J, Mirgain S, Coe CL, Bačkonja M. Mindfulness meditation and cognitive behavioral therapy intervention reduces pain severity and sensitivity in opioid-treated chronic low back pain: pilot findings from a randomized controlled trial. Pain Med 2016;17:1865–81.
[91] Zgierska AE, Ircink J, Burzinski CA, Mundt MP. Cost of opioid-treated chronic low back pain: findings from a pilot randomized controlled trial of mindfulness meditation-based intervention. J Opioid Manag 2017;13:169–81.