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 b,c, 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. 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. 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.

Pain is rarely managed effectively with pharmacological agents because of limited efficacy and dose-limiting adverse effects, leaving a significant unmet need for sufferers. 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.

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. Mindfulness-based interventions for chronic health problems involve multiple components, which can include...
systematic meditation training, patient education, yoga exercises, and group dialogue. 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.40,67 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.6 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 fash-ion.54,48,51,57 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.35 registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/PROS-PERO/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 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).

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 complete 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 <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.

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, fibromyalgia, chronic low back pain, diabetic peripheral neuropathy, chronic musculoskeletal pain, postherpetic neuralgia, HIV-associated chronic pain, failed back surgery syndrome, provoked localized vulvodynia, spinal cord injury with chronic pain, sickle cell disease with chronic pain, bladder pain syndrome, and medically unexplained pain. 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), mindfulness-oriented recovery enhancement (MORE), mindfulness-based cognitive therapy, mindfulness-oriented recovery enhancement (MORE), 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).

4.3. Excluded studies

We excluded 17 studies after the full articles were reviewed. 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.
| 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, 66 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; relaxation 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, 83 2002 | Fibromyalgia | 2 | TAU | Weekly sessions for 8 weeks | MBSR, n = 51; control, n = 40 |
| MBSR                     | Wells, 86 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 variation           | Cathcart, 12 2014 | Tension-type headache | 2                    | TAU           | Weekly sessions for 3  weeks | Treatment, n = 29; control, n = 29 |
| MBSR variation           | La Cour, 13 2015 | Varied                 | 2                    | TAU           | Weekly sessions for 8 weeks | Treatment, n = 54; control, n = 55 |
| MBSR variation           | Meize-Grochowski, 16 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, 25 2010 | Diabetic peripheral neuropathy | 2 | Nutrition 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-Delgado,54 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 6 weeks   | MORE, n = 57; control, n = 58 |
| MORE                                                          | Garland,30 2013     | Chronic noncancer pain | 2                     | Support group  | Weekly sessions for 6 weeks   | MORE, n = 50; control, n = 42 |
| Manualized meditation-CBT intervention ("mindfulness for chronic pain") | Zgierska,20 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,40 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,70 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 |

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

(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. 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, such as what percentage of participants were receiving opioid and nonopioid treatments for their chronic pain. A trial by Andrés-Rodriguez et al. investigated MBSR for fibromyalgia reported that of 66 participants, 34.8% were taking NSAIDs, 12.1% were taking anticonvulsants, 36.4% were taking antidepressants,
| 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, 2019 | Fibromyalgia           | No                                                  | Treatment group: 50.0% analgesics, 52.3% 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, 2015 | Chronic headache       | No                                                  | Not described                                                   | No                                               | No                                                             | Not reported |
| MBSR                     | Banth, 2015      | Low back pain          | No                                                  | Not described                                                   | No                                               | No                                                             | Not reported |
| MBSR                     | Cash, 2015       | Fibromyalgia           | No                                                  | Not described                                                   | No                                               | No                                                             | Not reported |
| MBSR                     | Chavooshi, 2016  | Medically unexplained pain | No                                                  | Not described                                                   | No                                               | No                                                             | Not reported |
| MBSR                     | Cherkin, 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, 2010      | Back pain, leg pain    | No                                                  | Not described                                                   | No                                               | No                                                             | Not reported |
| MBSR                     | George, 2017     | HIV-associated chronic pain | No                                                  | Not described                                                   | No                                               | No                                                             | Not reported |
| MBSR                     | Kanter, 2016     | Interstitial cystitis/ bladder pain syndrome | No                                                  | Not described                                                   | No                                               | No                                                             | Not reported |
| MBSR                     | Nathan, 2017     | Painful diabetic peripheral neuropathy | No                                                  | Not described                                                   | No                                               | No                                                             | Not reported |
| MBSR                     | Plews-Ogan, 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, 2011    | Fibromyalgia           | No                                                  | Not described                                                   | No                                               | No                                                             | Not reported |
| MBSR                     | Fibromyalgia     | No                                                  | No                                                  | No                                                             | No                                                             | No                                                             | Not reported |

(continued on next page)
| 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                     | Weissbecker, 2002 | Fibromyalgia           | No                                                 | Not described                                                 | No                                                            | No                                                                | Not reported |
| MBSR                     | Wells, 2014       | Migraines              | No                                                 | Incompletely described                                        | No                                                            | No                                                                | No adverse events occurred among participants |
| MBSR                     | Wong, 2009        | Unspecified            | No                                                 | Not described                                                 | No                                                            | No                                                                | Not reported |
| MBSR                     | Wong, 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, 2014    | Tension-type headache  | Yes                                                | N/a                                                           | N/a                                                           | N/a                                                               | Not reported |
| MBSR variation           | La Cour, 2015     | Varied                 | No                                                 | Incompletely described                                        | 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           | Meizer-Grochowski, 2015 | Postherpetic neuralgia | No                                                 | Not described                                                 | No                                                            | No                                                                | Not reported |
| MBSR variation           | Morone, 2016      | Low back pain          | No                                                 | Not described                                                 | No                                                            | No                                                                | No adverse events occurred among participants |

Table 2 (continued)
| 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, 25 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)
| 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, 2015         | Chronic noncancer pain | No                                                  | Incompletely described                               | No                                                  | No                                                            | Not reported |
|                          |                    |                        |                                                     | 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 | |
| MORE                    | Garland, 2014      | Chronic noncancer pain | No                                                  | Incompletely described                               | Yes                                                 | No                                                            | Not reported |
|                          |                    |                        |                                                     | 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 | Both groups required patients to be prescribed and have taken opioids for their pain | |
| MORE                    | Garland, 2013      | Chronic noncancer pain | No                                                  | Incompletely described                               | Yes                                                 | No                                                            | Not reported |
|                          |                    |                        |                                                     | 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 | Both groups required patients to be prescribed and have taken opioids for their pain | |
| Manualized meditation-CBT intervention, usual care, and opioid therapy | Zgierska, 2016     | Low back pain          | No                                                  | Incompletely described                               | Yes                                                 | No                                                            | Only anticipated, mild, and self-limited mild side effects were reported by the participants |
|                          |                    |                        |                                                     | Participants were treated with opioid therapy for 7.9 ± 5.7 years. | To be eligible, participants had to have been treated by a clinician with daily opioid therapy (at least 30 mg of morphine-related dose) for at least 3 months. | |
| Mindfulness-based pain management program | Brown, 2013        | Fibromyalgia, rheumatoid arthritis, osteoarthritis, and other musculoskeletal pain | No                                                  | Not described                                        | No                                                  | No                                                            | Not reported |

(continued on next page)
18.2% were taking opioids. A trial by Cherkin et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{60} that investigated a MBSR variation for low back pain reported that of 37

| 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,\textsuperscript{41} 2018 | Spinal cord injury | No | Not described | No | No | Not reported |
| Second-generation mindfulness-based intervention | Van Gordon,\textsuperscript{79} 2017 | Fibromyalgia | No | Not described | No | No | Not reported |
| Mindfulness-based group cognitive behaviour therapy | Guillet,\textsuperscript{39} 2019 | Provoked localized vulvodynia | No | Not described | No | No | Not reported |
| Brief mindfulness-based body scan | Ussher,\textsuperscript{78} 2014 | Unspecified | No | Treatment group: 55.6% opioids, 63.0% nonopioid analgesia, and 48.1% neuropathic analgesia | No | No | Not reported |
| Brief mindfulness-based intervention | Howarth,\textsuperscript{44} 2019 | Back pain and others | No | Not described | No | No | Not reported |
| 6-Week customized mindfulness-based intervention | Simmons,\textsuperscript{72} 2019 | Sickle cell disease with chronic pain | No | Not described | No | No | Not reported |
| Mindful socioemotional regulation intervention (Internet) | Davis,\textsuperscript{67} 2007 | Fibromyalgia | No | Not described | No | No | Not reported |
| Mindfulness awareness in body-oriented therapy | Price,\textsuperscript{57} 2007 | Unspecified | No | Not described | Yes | 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.
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 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 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 effects except one participant in the mindfulness-based cognitive therapy group who had spiritual issues possibly related to the treatment66; 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.

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 occurred69–71,82; one stated only mild and self-limited mild side effects were reported85; one stated that at least 2 participants experienced transient strong feelings of anger toward their pain condition and at least 2 participants experienced greater anxiety52; 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)15; one reported no significant adverse events except one participant in the mindfulness-based cognitive therapy group who had spiritual issues possibly related to the treatment66; 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 effects except one participant in the mindfulness-based cognitive therapy group who had spiritual issues possibly related to the treatment66; 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 2. Risk of bias graph: Review the authors’ judgement about each risk of bias item presented as percentages across all included studies.
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. Mindfulness-based interventions have also been shown to moderate the relationship between pain intensity and pain catastrophizing. 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.

The rational combination of psychotherapy and pharmacotherapy has been studied in many other medical contexts. A meta-analysis by Cuijpers et al. 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. 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). Studies have also suggested that psychotherapy combined with pharmacotherapy was more acceptable to patients than pharmacotherapy alone. 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] André-Rodríguez L, Borrás X, Feliu-Soler A, Pérez-Aранda A, Rozadilla-Sacanel L, 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, Dery 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;30:2567–62.
[5] Balshnahi NM, Amirani A, Haharakpoor 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, Sadowsky 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 DJ, Carmody J, Segal ZV, Abbey S, Specia M, Velling 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;1:2012:7.
[10] Brown CA, Jones AK. Psychobiological correlates of improved mental balance through education. N Engl J Med 2016;374:301–3.
[11] 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.
[12] Burger 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.
[13] Bishop SR, Lau M, Shapiro S, Carlson L, Anderson DJ, Carmody J, Segal ZV, Abbey S, Specia M, Velling D. Mindfulness: a proposed operational definition. Clin Psychol Sci Pract 2004;11:230–41.
[14] Borsook D. A future without chronic pain: neuroscience and clinical research. Cerebrum 2012;1:2012:7.
[15] Brown CA, Jones AK. Psychobiological correlates of improved mental balance through education. N Engl J Med 2016;374:301–3.
[16] 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.
[17] Burger 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.
[18] Bishop SR, Lau M, Shapiro S, Carlson L, Anderson DJ, Carmody J, Segal ZV, Abbey S, Specia M, Velling D. Mindfulness: a proposed operational definition. Clin Psychol Sci Pract 2004;11:230–41.
[19] Borsook D. A future without chronic pain: neuroscience and clinical research. Cerebrum 2012;1:2012:7.
[20] Brown CA, Jones AK. Psychobiological correlates of improved mental balance through education. N Engl J Med 2016;374:301–3.
[21] 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.
[22] Burger 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.
[23] Bishop SR, Lau M, Shapiro S, Carlson L, Anderson DJ, Carmody J, Segal ZV, Abbey S, Specia M, Velling D. Mindfulness: a proposed operational definition. Clin Psychol Sci Pract 2004;11:230–41.
[24] Borsook D. A future without chronic pain: neuroscience and clinical research. Cerebrum 2012;1:2012:7.
[25] Brown CA, Jones AK. Psychobiological correlates of improved mental balance through education. N Engl J Med 2016;374:301–3.
[26] 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.
[27] Burger 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.
[28] Bishop SR, Lau M, Shapiro S, Carlson L, Anderson DJ, Carmody J, Segal ZV, Abbey S, Specia M, Velling D. Mindfulness: a proposed operational definition. Clin Psychol Sci Pract 2004;11:230–41.
[29] Borsook D. A future without chronic pain: neuroscience and clinical research. Cerebrum 2012;1:2012:7.
[30] Brown CA, Jones AK. Psychobiological correlates of improved mental balance through education. N Engl J Med 2016;374:301–3.
[31] 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.
[32] Burger 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.
[33] Bishop SR, Lau M, Shapiro S, Carlson L, Anderson DJ, Carmody J, Segal ZV, Abbey S, Specia M, Velling D. Mindfulness: a proposed operational definition. Clin Psychol Sci Pract 2004;11:230–41.
[34] Borsook D. A future without chronic pain: neuroscience and clinical research. Cerebrum 2012;1:2012:7.
[35] Brown CA, Jones AK. Psychobiological correlates of improved mental balance through education. N Engl J Med 2016;374:301–3.
[36] 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.
[37] Burger 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.
[38] Bishop SR, Lau M, Shapiro S, Carlson L, Anderson DJ, Carmody J, Segal ZV, Abbey S, Specia M, Velling D. Mindfulness: a proposed operational definition. Clin Psychol Sci Pract 2004;11:230–41.
[39] Borsook D. A future without chronic pain: neuroscience and clinical research. Cerebrum 2012;1:2012:7.
[40] Brown CA, Jones AK. Psychobiological correlates of improved mental balance through education. N Engl J Med 2016;374:301–3.
[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] Heem 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] Hefner 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;25:5205.

[43] Hilton L, Hempel S, Eving BA, Apaydın E, Xenakis L, Newburry S, Colaiaco B, Mahler AR, Shamman RM, Sorbero ME, Maglione MT. 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: randomised controlled trial. Medicine (Baltimore) 2016;95:393495.

[46] Johanssen M, O’Connor M, O’Toole MS, Jensen AS, Hajirs I, Zacharias 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;34:3930–9.

[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;4:32–47.

[48] Kaiser U, Treede RD. Effects of mindfulness meditation on chronic pain: a randomized controlled trial. Pain Med 2008;10:735–43.

[49] Kaur E, Treede RD, Sabatowski R. Multimodal pain therapy in chronic neuropathy. Clin Diabetes 2017;35:294–304.

[50] Kanter G, Komesu YM, Qaedan F, Jeppson PC, Dunivan GC, Cichowski K, Lauria G, Treede RD, Sabatowski R. Multimodal pain therapy in chronic neuropathy in adults older than 50 years. Holist Nurs Pract 2017;31:148–52.

[51] Karteris E, Albenque M, Dizadji B, Li X, Anumolu L, Samaan N, Talbot N, Moynihan J, sacharova J, Scheidt P, others. Mindfulness training reduces fear-avoidance beliefs about work-related activity: randomised controlled trial. Pain Med 2019;20:1767–83.

[52] Kass N, 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: randomised controlled trial. Medicine (Baltimore) 2016;95:393495.

[53] 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;4:32–47.

[54] Kaiser U, Treede RD. Effects of mindfulness meditation on chronic pain: a randomized controlled trial. Pain Med 2008;10:735–43.

[55] Kaur E, Treede RD, Sabatowski R. Multimodal pain therapy in chronic neuropathy. Clin Diabetes 2017;35:294–304.

[56] Kammen K, Vowsey 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. Psychohol Med 2017;47:414–25.

[57] Kanter G, Komesu YM, Qaedan F, Jeppson PC, Dunivan GC, Cichowski K, Lauria G, Treede RD, Sabatowski R. Multimodal pain therapy in chronic neuropathy in adults older than 50 years. Holist Nurs Pract 2017;31:148–52.

[58] Park R, Mohiutdin M, Poulin P, Salomon 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.

[59] Piarra-Delgado M, Latorre-Postigo JM. Effectiveness of mindfulness-based cognitive therapy in the treatment of fibromyalgia: a randomised controlled trial. Cogn Ther Res 2013;37:1015–26.

[60] Ploews-Ogan M, Owens JE, Goodman M, Wolfe P, Schorning 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.

[61] Poulin PA, Romanow HC, Rabhari 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.

[62] 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.

[63] Reiner K, Tisi L, Lipitz D. Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. Pain Med 2013;14:230–42.

[64] 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.

[65] 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.

[66] 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.

[67] Stead LF, Kolpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2016;CD006286.

[68] Steurer J. Mindfulness-based stress reduction is effective in patients with chronic lumbar backache [in German]. Praxis (Bern) 2014;106:705–721–2.

[69] 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.

[70] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoile 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, Vaeyen 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.

[71] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoile 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, Vaeyen JWS, Wang SJ. A classification of chronic pain for ICD-11. PAIN 2015;166:1003–7.

[72] Ussher M, Spatz A, Copland C, Nicolau 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.

[73] Van Gordon W, Shonin E, Dunn T, 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.

[74] Weiss RD, Kuepferbender KD. Combining psychosocial treatment with pharmacotherapy for alcohol dependence. J Clin Psychopharmacol 2000;20(2, suppl 1):S75-10.

[75] 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 Psychosomatics 2002;9:297–307.

[76] Wells RE, Burch R, Paulsen RL, Wayne PM, Houlé TT, Loder E. Meditation for migraines: a pilot randomized controlled trial. Headache 2014;54:1484–95.

[77] Wisciberg RF, Zale EL, Heinhuu TJ, Ozkan S, Nazzal AL, 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, Kicke 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, Kicke 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.