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Mindfulness-Based Cognitive Therapy for Treating Chronic Pain A Systematic Review and Meta-analysis

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ABSTRACT

Chronic pain is a significant public health problem with emotional and disabling factors, which may not completely respond to current medical treatments such as opioids. The systematic review and meta-analysis aimed to examine the effectiveness and safety of MBCT for patients with chronic pain. Database searches of PubMed, Medline, EMBASE, the Cochrane Library, PsycINFO, Web of Science, Scopus and CINAHL up to 15 October 2019. Included studies assessed with the Cochrane risk-of-bias tool. Eight RCTs involved 433 patients, including chronic low back pain, fibromyalgia, migraine, rheumatoid arthritis and mix etiology. MBCT intervention demonstrated a short-term improvement on depression mood [standardized mean difference -0.72 ; 95% confidence interval $= -1.22$ to -0.22 , $p = 0.005$] compared with usual care and was associated with short-term improvement in mindfulness compared with non-MBCT [SMD 0.51 ; 95% CI $= 0.01$ to 1.01 , $p = 0.04$]. Between-group differences in pain intensity, pain inference and pain acceptance were not significant at short- or long-term follow-up. Compared to active treatments, MBCT intervention not found significant differences in either short- or long-term outcomes. MBCT showed short-term efficacious on depressed mood and mindfulness of chronic pain patients. Longer follow-ups, large sample and rigorous RCTs that can be best understand remaining uncertainties needed.

ARTICLE HISTORY

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KEYWORDS

Chronic pain; meta-analysis; mindfulness-based cognitive therapy; review

Introduction

Chronic pain is a common public health problem that has an impact on physical disability, emotion (depression and anxiety) and quality of life (Institute of Medicine Committee on Advancing Pain Research C, E, 2011; Kawai et al., 2017). Approximately 12% to 25% of the population in the United States (US) and Europe and 34%–42% of patients in low-and middle-income have chronic pain (Center for Health Statistics

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N. Health, U. S, 2006; Institute of Medicine Committee on Advancing Pain Research C, E, 2011; Jackson et al., 2016; Kawai et al., 2017). In the past 20 years, opioids been frequently used for chronic pain, but their long-term efficacy is limited and always be accompanied by severe medicine addition (Boudreau et al., 2009; Dowell et al., 2016). The high prevalence and refractory nature of chronic pain combined with the negative consequences of pain medication dependence have led to increased interest in treatment planning, including adjunctive therapies or alternatives to medication (Chiesa & Serretti, 2011).

As an increasingly popular chronic pain self-management technique, the mindfulness-based intervention has great potential. In recent years, mindfulness-based cognitive therapy (MBCT) has been receiving growing attention. MBCT integrates key elements from cognitive-behavioural technique (CBT) and mindfulness-based stress reduction (MBSR) directly target cognitive mechanism, which implicates how individuals respond to the experience (Daniel, 2013; Segal, 2002; Teasdale et al., 2000). Primary evidences support MBCT as a treatment for depression (Teasdale et al., 2000). In addition, an increasing body of evidence supports the efficacy of MBCT for other conditions (Mansourishad & Borjali, 2017; Parra-Delgado & Latorre-Postigo, 2013).

Several studies reported the beneficial efficacy of MBCT on patients with chronic pain (Dalili & Bayazi, 2019; De Jong et al., 2018; Parra-Delgado & Latorre-Postigo, 2013). A systematic review of 25 RCTs suggested that mindfulness-based interventions for chronic pain are, on the whole, associated with a significant improvement in a number of outcomes compared with other treatments (Veehof et al., 2016). However, the previous review included other acceptance-based interventions rather than MBCT intervention and was therefore not directly comparable (Veehof et al., 2016). Hence, we do not know whether MBCT is differentially efficacious for chronic pain. The current analysis designed to examine the effectiveness and safety of MBCT for patients with chronic pain on clinical and humanistic outcomes, compared with usual care or active comparators across randomized-controlled trials at short- or long term follow-up.

Method

The review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Moher et al., 2009) and the recommendations of the Cochrane Collaboration (Cumpston et al., 2019).

Data sources and searches

Searched electronic databases including PubMed, Medline, EMBASE, the Cochrane Library, PsycINFO, Web of Science and Scopus from inception through 15 October 2019. The following search keywords used (mindfulness-based cognitive therapy) OR (mindfulness-based cognitive therapy) OR (MBCT), without English language or other restrictions. The reference lists of relevant original articles, selected reviews and textbooks checked manually to retrieve potential eligible studies. Also, conducted grey literature research for other organizations' websites.

Study selection

Studies included met following criteria: (1) study design: randomized controlled trials of MBCT for chronic pain or chronic pain-related conditions; (2) participants: age 18 or older, participants met the diagnostic criteria for IASP chronic pain; (3) interventions: studies were required to come from the original MBCT program with a program length of at least 4 weeks; (4) control group: at least a usual care/waitlist or an active comparator (mindfulness meditation or psychoeducation et al.); (5) outcome measures: pain intensity or depression as the primary outcome; (6) there was no significant change in concomitant medications or other treatments during the interventions.

Studies excluded: (1) published by repeat or not obtained full-articles; (2) in order to minimize heterogeneity in the sample, excluded patients with malignant pain.

Two reviewers independently screened all of the retrieved citations in accordance with the inclusion criteria. Discrepancies rechecked by consensus.

Data extraction and quality assessment

The two reviewers independently using a standardized form, including study characteristics, participants, interventions and outcome measures at short- or long term follow-up also performed data extraction. In eight relevant studies, one study had three arms and the other seven had two arms. The 3-arms trial had two non-MBCT arms: one treatment as regular care with mindfulness meditation and the other treatment as regular care with cognitive therapy. The Cochrane risk-of-bias tool used to assess the risk of bias (Cumpston et al., 2019). Discrepancies resolved by a third reviewer or consensus reached by further discussion.

Data analysis and synthesis

We examined the effectiveness and safety of MBCT for patients with chronic pain compared with non-MBCT, usual care or active treatment group. Pain intensity or depression was involved as the primary outcome. Secondary outcomes included mindfulness, pain acceptance and pain interference. Only two studies reported long term follow-up outcomes between MBCT and other active comparators. We also analyzed short- and long-term outcomes individually. In this review, outcomes measured post-intervention defined as short term follow-up and that measured after completing treatment about 6 months defined as a long term follow-up.

Standardized mean differences (SMDs) and 95% confidence intervals (CIs) calculated as an effect size measure between groups in means divided by the pooled SD, using the Hedges' g formula (Cumpston et al., 2019). If SDs not obtained, they calculated from SEs and CIs. For pain intensity or depression, negative SMDs mean beneficial effects for MBCT group vs control group. For pain interference, pain acceptance and mindfulness, positive SMDs indicated beneficial effects of MBCT intervention.

For 3-arms trial, the two control groups were combined when analysis of MBCT vs active comparator was conducted. Outcome data also combined when studies presented only subgroup data. Due to the diversity of the chronic pain conditions and comparators, random-effects applied. All analysis conducted using Stata 13.0. Heterogeneity between

studies assessed using I^2 -statistic. I^2 statistics greater than 75% indicated as significant heterogeneity (Cumpston et al., 2019).

Results

A total of 5305, titles were identified as potentially relevant studies, from which eight studies were eligible for inclusion in this review (Dalili & Bayazi, 2019; Day et al., 2014, 2019; De Jong et al., 2018; Dowd et al., 2015; Mansourishad & Borjali, 2017; Parra-Delgado & Latorre-Postigo, 2013; Wang et al., 2016) (Figure 1).

Characteristics of primary studies

Characteristics of the eight studies included in this review displayed in Table 1. Studies, respectively, have done in the US, Iran, China, Ireland and Spain. The mean age of 433 participants ranged from 34 to 53 years, except those from two studies (no age available). The majority of participants were female and given face-to-face interventions (exception of one study). For participants involved in all studies, the pain lasted three or more months, which was, respectively, chronic low back pain, fibromyalgia, migraine, chronic headache pain, rheumatoid arthritis and mix etiology.

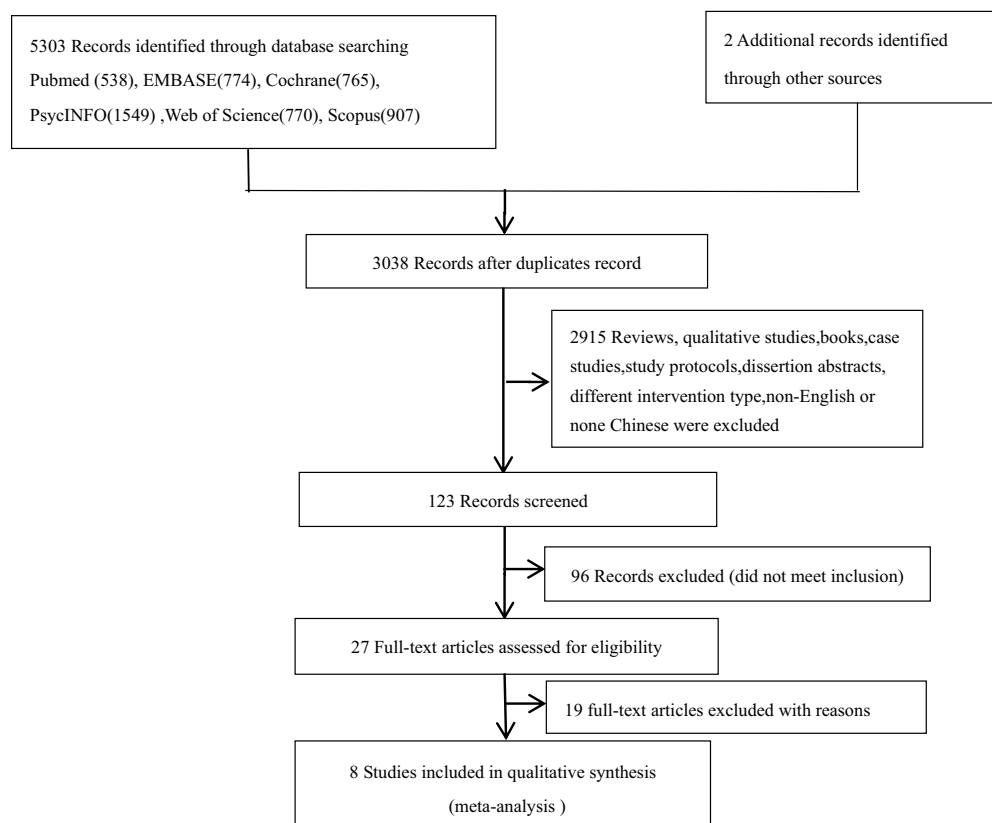


Figure 1. Flow chart of studies search.

Table 1. Characteristics of the included studies.

Study/year (Reference)	Country	Mean Age (SD),y	Participants (Groups),n	Chronic pain Population	Intervention Length,Frequency,and Duration		
					Treatment Group	Comparison Group	
Dallili & Bayazi, 2019	Iran	–	28(2)	Rheumatoid Arthritis	MBCT according to method developed by Segal et al 8-wk course, once weekly for 2 h sessions Homework:Frequency and duration not mentioned	regular care	
De Jong et al., 2018	US	Overall 50.7 (11.4)	40(2)	Mixed aetiology	MBCT according to method developed by Segal et al 8-wk course, once weekly for 2 h sessions Homework:Frequency and duration not mentioned	Waitlist Additional TAU allowed	
Mansourishad & Borjali, 2017	Iran	MBCT:33.6(6.2) CG:30.7(5.2)	26(2)	Migraine Headaches	Additional TAU allowed MBCT according to method developed by Segal et al 8-wk course, once weekly for 2 h sessions Homework: every day	Only UC	
Wang et al., 2016	China	–	77(2)	Mixed aetiology	MBCT according to method developed by Segal et al 8-wk course, once weekly for 2 h sessions Homework:30 min,3d per week Additional UC allowed	Only UC	
Dowd et al., 2015	Ireland	Overall 44.53 (12.25)	124(2)	Mixed aetiology	MBCT according to method developed by Segal et al On-line 6-wk course, twice per weekly Homework:20 min daily	psychoeducation 6-wk programs	
Day et al., 2014	US	Overall 42(12)	36(2)	Headache Pain	MBCT according to method developed by Segal et al 8-wk course, once weekly for 2 h sessions Homework:45 min,6d per week Additional regular care allowed	DT Additional regular care allowed	
Parra- Delgado & Latorre- Postigo, 2013	Spain	Overall 52.67(10.08)	33(2)	Fibromyalgia	MBCT according to method developed by Segal et al 3-mo course, 2.5 h 8 sessions Homework: 6d per week Additional regular care allowed	Only UC Additional regular care allowed	

(Continued)

Table 1. (Continued).

Study, year (Reference)			Intervention Length, Frequency, and Duration			
	Country	Mean Age (SD), y	Participants (Groups), n	Chronic pain Population	Treatment Group	Comparison Group
Day et al., 2019	US	Overall 50.74(14.43)	69(3)	Chronic Low Back Pain	MBCT according to method developed by Segal et al 8-wk course, once weekly for 2 h sessions Homework: 45 min, 6d per week Additional regular care allowed	1. CT according to Thom's approach 8-wk program Homework: every day Additional regular care allowed 2. MM according to Day' s MBCT 8-wk program Homework: 45 min daily Additional regular care allowed
Minimum to define complete 4 sessions			ITT		Posttreatment assessment points	Outcome measures
4 sessions			No	Postintervention: week 8		Depression (DASS-21)
			Yes	Postintervention: week 8		Depression (QIDS-C16)
Not stated			No	Postintervention: week 8 Follow -up: 3 mo		Pain interference (BPI)
Not stated			No	Postintervention: week 8		Pain intensity (VAS)
						(11-point Likert scale)
Not stated			Yes	Postintervention: week 8 Follow -up: 6 mo		Mindfulness((FFMQ)
						Depression(POMS)
						Depression(HADS)
						Pain interference (BPI)
						Mindfulness(MASS)
4 sessions			Yes	Postintervention: week 8		Pain Acceptance (CPAQ)
						Pain Catastrophizing (PCS)
						Pain interference (BPI)
						Pain intensity(BPI)
						Mindfulness(MASS)
4 sessions			No	Postintervention: week 8 Follow -up: 3 mo		Pain Acceptance (CPAQ)
						Pain Catastrophizing (PCS)
4 sessions			Yes	Postintervention: week 8 Follow -up: 3 mo Follow -up: 6 mo		Depression(BDI)
						Pain intensity (VAS)
						Pain intensity (NRS)
						Pain interfere (PROMIS)
						Depression (PROMIS)

Abbreviations: MBCT = Mindfulness-Based Cognitive Therapy; MM = Mindfulness Meditation; CT = Cognitive therapy; DASS-21 = Depression Anxiety Stress Scales; TAU = Treatment as usual; QIDS-C16 = Quick Inventory of Depressive Symptomatology – Clinician rated; BPI = Brief Pain Inventory; VAS = Visual Analogue Scale; CPAQ = Chronic Pain Acceptance Questionnaire; PCS = Pain Catastrophizing Scale; UC = usual care; FFMQ = Five-Facet Mindfulness Questionnaire; POMS = Profile of Mood States; HADS = The Hospital Anxiety and Depression Scale; MASS = Mindful Attention Awareness Scale; DT = delayed treatment; BDI = Beck Depression Inventory; NRS = 11-point numerical rating scale; PROMIS = Patient-Reported Outcomes Measurement Information System

All studies involved MBCT intervention according to the method developed by Segal et al. Six RCTs used MBCT programs and consisted of eight weekly 2 h sessions. One trial modified the 8-week course by held weekly 2.5 h instead of 2-h sessions. In Dowd's study, an on-line MBCT intervention held, which consisted of twice per week for 6 weeks. Of all 433 participants, 193 patients evaluated at six-month follow-up.

Four studies used usual care alone as the comparison group, one used a waitlist group and one used delayed treatment group as the control group. Two trials compared MBCT with active comparators that included psychoeducation, mindfulness meditation and cognitive therapy. In all studies, the session length and frequency of MBCT groups and the control groups matched.

Risk of bias and study quality

Table 3 presents the risk of bias for each of the trials. The risk of selection bias judged as low in six studies. The random sequence generation was unclear in one study and three trials did not generate a sufficient form of allocation concealment. No, RCT blinded participants because of the nature of the treatment. Four studies presented blind of outcome assessment. Other studies have shown that outcome assessors either not blinded or not mentioned. The risk of reporting bias and other bias was low in all studies except for one study. Intention to treat (ITT) analysis conducted in four studies. Three RCTs judged as high-risk studies. No, trial excluded in this review but considered when analyzing statistic heterogeneous.

Risk of bias across studies

Due to the limited number of studies, the ability to assess the publication bias by the funnel plot proved unsuccessful (Egger et al., 1997).

Table 3. Risk-of-bias assessment.

Study, year (Reference)	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants And person- nel (Performance Bias)	Blind of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attribution Bias)	Selective Reporting (Reporting Bias)	Other Bias
Dalili & Bayazi, 2019 ^[15]	Low risk	Low risk	High risk	Unclear	Low risk	Low risk	Low risk
De Jong et al., 2018 ^[14]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Mansourishad & Borjali, 2017 ^[12]	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk
Wang et al., 2016^[19]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Dowd et al., 2015 ^[21]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Day et al., 2014 ^[22]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Parra- Delgado & Latorre-Postigo 2013 ^[13]	Low risk	unclear	unclear	unclear	High risk	unclear	Low risk
Day et al., 2019 ^[20]	Low risk	Low risk	High risk	Low risk	Low risk	low risk	Low risk

Effects on primary outcomes

Depression

In comparison, with usual care, MBCT demonstrated a short term statistically significant improvement in depression [4RCTs; SMD -0.72, 95%CI = -1.22 to -0.22, I^2 55.5%, $p = 0.005$] (Figure 2). Unfortunately, no studies assessed a long term follow-up comparing MBCT with usual care. No, statistically significant was found in depression in favour of MBCT compared to other active treatments at either short- or long term follow-up (Figure 2).

Pain intensity

There was no statistically significant difference in pain intensity between MBCT and usual group [5RCTs; SMD -0.28,95%CI = -0.56 to 0.01, I^2 0%, $p = 0.06$] or active comparator [2 RCTs; SMD -0.01,95%CI = -0.75 to 0.74, I^2 68%, $p = 0.99$] at short term follow-up. MBCT was also demonstrated not statistically significant [2RCTs; SMD 0.42, 95%CI = -0.6 to 1.44, I^2 82.5%, $p = 0.42$] in comparison with active comparator at long term follow-up (Figure 3).

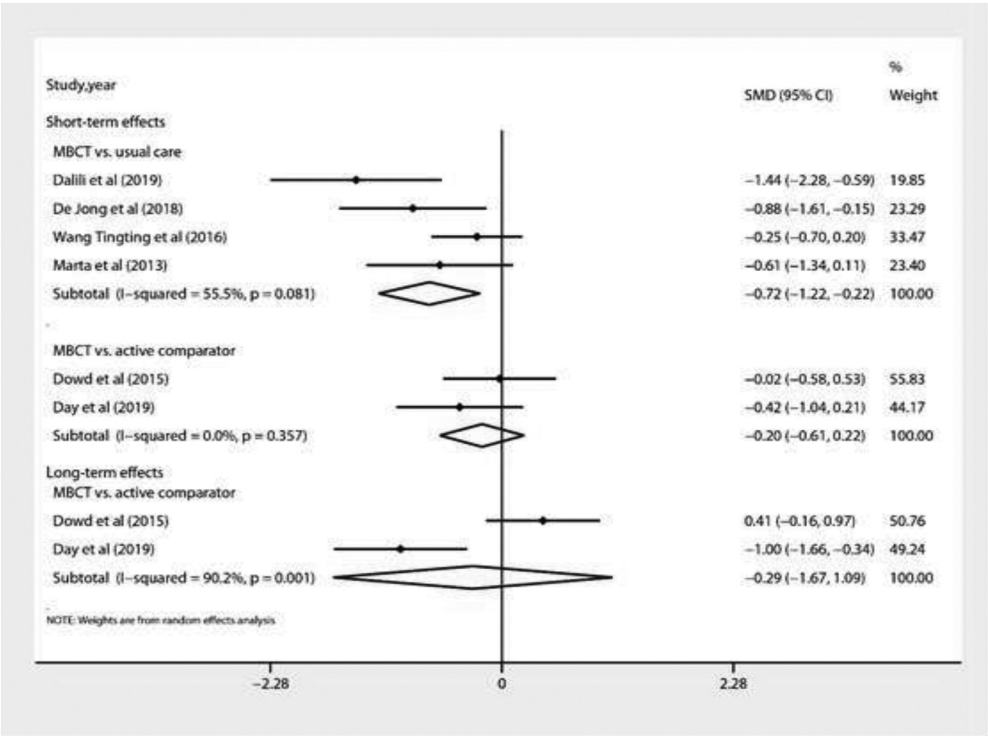


Figure 2. Meta-analysis of depression.

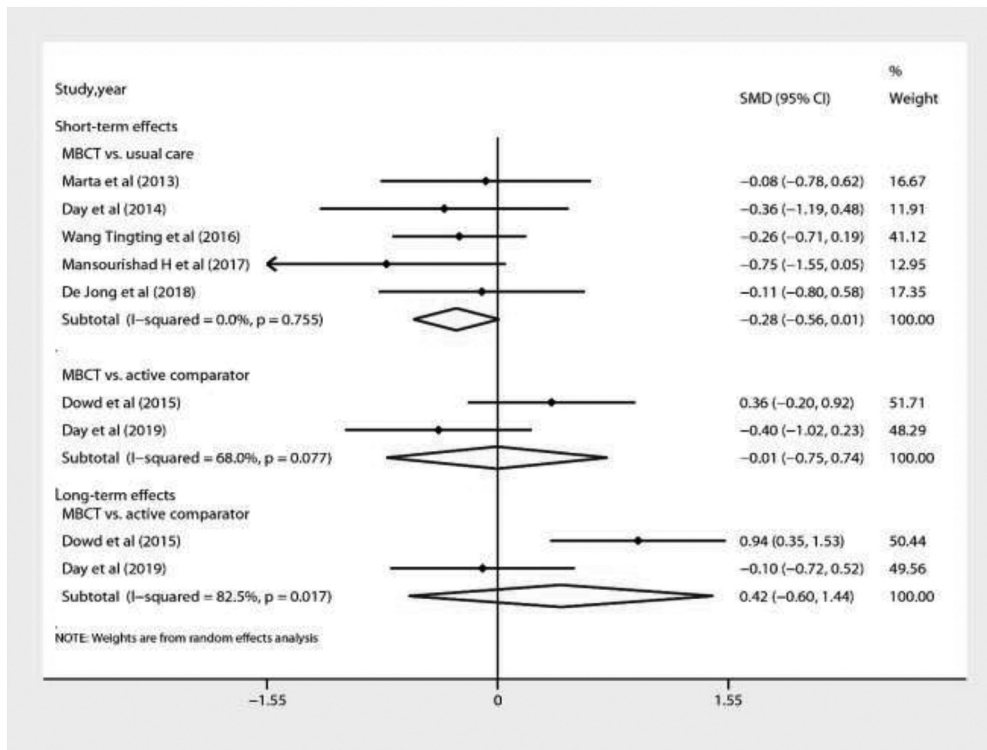


Figure 3. Meta-analysis of pain intensity.

Effect on secondary outcomes

Mindfulness

The effect was found on mindfulness, in favour of MBCT compared to non-MBCT interventions in the short term [3 RCTs; SMD 0.51, 95%CI = 0.01 to 1.01, I^2 51.5%, $p = 0.04$] (Table 4).

Pain interference

For pain interference, no statistically significant short-term effects were found in comparison of MBCT and usual care [2 RCTs; SMD -0.49, 95%CI = -1.27 to 0.3, I^2 50.1%, $p = 0.22$] or active comparators [2 RCTs; SMD -0.16, 95%CI = -0.57 to 0.26, I^2 0%, $p = 0.45$]. At 6-month follow-up, MBCT was also documented not statistically significant [2 RCTs; SMD -0.29, 95%CI = -1.29 to 0.71, I^2 81.8%, $p = 0.56$] compared with active control group (Table 4).

Pain acceptance

Only two trials assessed short-term pain acceptance and there was no statistically significant difference between groups [2 RCTs; SMD 0.14, 95%CI = -0.28 to 0.56, I^2 0%, $p = 0.51$] (Table 4).

Table 4. Effect on secondary outcomes: mindfulness, pain inference and pain acceptance.

Outcome	Standardised mean difference	95% CI	P-value	I^2	Number of trials	Number of participants
Mindfulness(short-effects) (MBCTvs non-MBCT)	0.51	0.01 to 1.01	0.04	51.5%	3	151
Pain interference(short-effects) MBCT vs usual care	-0.49	-1.27 to 0.3	0.22	50.1%	2	57
Pain interference(short-effects) MBCT vs active comparator	-0.16	-0.57 to 0.26	0.45	0%	2	93
Pain interference(long-effects) MBCT vs active comparator	-0.29	-1.29 to 0.71	0.56	81.8%	2	93
Pain acceptance (long-effects) MBCT vs active comparator	0.14	-0.28 to 0.56	0.51	0%	2	89

Adverse events

Two studies reported adverse events and no serious adverse events occurred. One RCT reported one participant had a spiritual problem during MBCT intervention, maybe related to the treatment. Another trial reported that adverse events occurred in five participants (one in mindfulness meditation, two in cognitive therapy, two in MBCT) but all events were considered unrelated to interventions.

Discussion

The paper is updated with a specific focus on the effectiveness and safety of MBCT for patients with chronic pain. The meta-analysis provides limited evidence that MBCT intervention may be effective on depression compared with usual care and has a positive impact on mindfulness compared with non-MBCT in the short term. Between-group differences in pain intensity, pain inference and pain acceptance were not significant at short- or long term follow-up. The studies in this review were few. All long term follow-up results need interpreting cautiously since the results are reflected on two RCTs that had considerable heterogeneity (Day et al., 2019; Dowd et al., 2015). The current data demonstrates limited evidence to understand the effectiveness of MBCT in chronic pain.

The findings of the current literature are partly in line with two prior meta-analyses that included other mindfulness-based interventions, which show significant effects on depression (Hilton et al., 2017; Veehof et al., 2016). To note, statistically significant change in pain intensity not demonstrated in this review, which was consistent with the result of a meta-analysis of mindfulness-based interventions (Bawa et al., 2015). Other studies have shown that the aim of mindfulness-based interventions is not to reduce or remove pain intensity instead of increasing acceptance of pain (Veehof et al., 2016). It remains unclear whether this result is due to a power problem or fundamental outcome of the effect of MBCT on chronic pain. In addition, it was somewhat surprising that this review also did not find evidence of either short- or long term statistically significant improvement in pain inference. However, it is notable that some initial evidence reported pain cognitive influenced by meditation (Zeidan et al., 2012) and greater self-reported cognitive intrusion of pain was significantly associated with higher levels of pain interference in activities of daily living (Talaie-Khoei et al., 2017). Whether this result reflects weaknesses in the primary trials' survey instruments or whether MBCT could change pain self-cognitive of patients with chronic pain is unclear.

The various types of therapists, which might introduce a degree of bias, delivered all MBCT programs. Studies that employed suitably qualified therapists (e.g., MBCT accredited therapists, clinical/counselling psychologists) will be higher quality. In the meta-analysis, only five studies indicated that the instructors received training from professional organizations. In addition, fidelity to the treatment model needs reassessment. No trials included in the review found that study investigator monitored instructors' adherence to the treatment model. Clearly, it is necessary to ensure the effectiveness of treatment. Further intervention reassessment completed (e.g., supervision, use of recordings, etc.).

Outcome measurement and study results also varied. In addition, the chronic nature of pain, there were some of the heterogeneity in conditions within the studies. Usually, chronic pain normally explained by central sensitization and the gate control theory of pain. However, in the case of a condition like Rheumatoid Arthritis (RA), the primary cause of pain is a chronic inflammation of joints and musculoskeletal tissue. As a result, normal healing does not take place. Some studies indicated that central sensitization can occur in RA, but it is considered a secondary cause of pain and would not apply to all patients. This makes RA potentially very different from chronic pain of unknown etiology, back pain, etc. In addition, a study using depression as a primary outcome probably might include primarily patients with depressive symptoms or concomitant depression (De Jong et al., 2018). Due to these variations, the random-effect model selected in the analysis. However, there were no sufficient numbers of studies to explore this heterogeneity in depth.

Homework practice was an important aspect of MBCT but two RCTs did not mention homework frequency and duration. It was unclear whether participants implemented daily home practice as recommended. Frequency and duration of practice may affect outcomes (Pradhan et al., 2007). Therefore, we advise future researches should provide detailed actual individual homework frequency and duration and evaluate their effects. Although two trials indicated that pain acceptance increased after MBCT interventions, none of the between-group differences shown to be significant in the pooled analysis (figure 6). Moreover, whether pain acceptance could explain substantial variance in any of the standard measures was still unclear and yet to be further examined (Masedo & Esteve, 2007; McCracken, 1998; Hann & McCracken, 2014; Zeidan et al., 2012). Finally, only two studies reported rare and no serious adverse events, limiting our comprehensive assessment of the safety of MBCT interventions for chronic pain patients. Further investigations should collect detailed adverse event data.

Nevertheless, several limitations have taken into account in this review. Firstly, the number of studies included was small, with some of the pooled analysis based on only two trials, especially follow-up analysis. Secondly, some RCTs had their own limitations. Only two RCTs had a sample size greater than 40 per group and intention-to-treat (ITT) analysis conducted on only four studies. Three RCTs judged as high-risk studies. Thirdly, these studies had variables in terms of their participants' sociodemographic characteristics and we did not standardize these variables due to the limitation of data available. Thus, there was not sufficient evidence to evaluate whether the results of this review influenced by participants sociodemographic characteristics. Finally, as with some other review, maybe there were studies published by non-English and Chinese or unpublished studies were not able to evaluate.

Conclusion

Current evidence suggests that MBCT showed short-term efficacious on depressed mood and mindfulness of chronic pain patients. Although it is several limitations, the appropriate treatment for chronic pain is lacking. Given the high prevalence and often comorbid with depression of chronic pain, plus the negative consequences of pain medication dependence, the convenience, low-cost intervention and rare adverse events make it a self-management option for chronic pain, especially in patients with depression.

Suggest future studies perform dose–response analysis to determine the optimal amount of MBCT and search treatment mechanism and moderators of MBCT for chronic pain. Simultaneously, extend follow-up time, increase sample size, report detailed adverse events and collect key background variables (e.g., sociodemographic characteristics). Furthermore, many people suffering from chronic pain struggle with limitations in their daily life (Institute of Medicine Committee on Advancing Pain Research C, E, 2011; Kawai et al., 2017), but there is a very little study to apply functioning or disability as a primary outcome. Also, suggestions for future MBCT intervention trials to apply functioning or disability as the primary outcome.

Disclosure statement

The authors declare no competing interests.

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Author contributions

Ju-Hong Pei and Tong Ma conceived, designed and carried out the study, and the relevant data analysis and interpretation; Ju-Hong Pei and Tong Ma contributed equally to this work. Rui-Lin Nan and Hai-Xia Chen and carried out the study, the relevant data analysis and interpretation. Ya-Bin Zhang and Lin Gou contributed to the data analysis and interpretation. Xin-Man Dou: study design, methodological quality assessment, and preparation of the manuscript. All authors contributed to the writing and reviewing the final manuscript.

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