

# BMJ Open Mindfulness-based stress reduction (MBSR) as sole intervention for non-somatisation chronic non-cancer pain (CNCP): protocol for a systematic review and meta-analysis of randomised controlled trials

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## ABSTRACT

**Introduction:** Chronic non-cancer pain (CNCP) affects up to 50% of the world's population. It impacts negatively on quality of life; entailing high costs on our medical systems, and translates to economic burden due to work loss. Aetiology of CNCP is complex and multifactorial, embracing the somatosensory, cognitive and affective domains. Opioid analgesia and other invasive interventions are often inadequate for clinical management of CNCP. Recently, mindfulness-based stress reduction (MBSR) has become a popular therapy for various medical conditions, including CNCP. However, studies reported varying efficacies, and relevant systematic reviews have included clinical trials with inherent heterogeneity either in study conditions or types of interventions used. Our study aims to provide an updated and more critical evaluation of the efficacy of MBSR as the intervention for non-somatisation CNCP.

**Methods and analysis:** A systematic review with meta-analysis of randomised controlled trials published in English will be performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines and the Cochrane Collaboration format. MEDLINE, EMBASE, PsychINFO, and the Cochrane Central Register of Controlled Trials Intervention, will be searched independently by reviewers using defined MeSH terms. Studies with full texts using MBSR as the main intervention on patients with non-somatising CNCP will be included. Outcome measures include pain scores and disability assessment scales. Continuous data will be meta-analysed using the RevMan 5 Review Manager programme. Primary analysis will adopt the random effects model in view of heterogeneity between trials. The standardised mean difference will be expressed as the effect size with 95% CIs. Forest plots, funnel plots, the I<sup>2</sup> statistic and the Cochrane Risks of Bias Assessment table will be included.

**Ethics and dissemination:** No ethics approval is deemed necessary. Results of this study will be disseminated via peer-reviewed publications and scientific meetings.

## Strengths and limitations of this study

- Compared with similar publications, our study aims to provide an update and more critical evaluation on the critical efficacy of mindfulness-based stress reduction (MBSR) as the main intervention for non-somatising chronic non-cancer pain.
- The study will provide useful evidence-based guidance for healthcare providers and policy stakeholder to facilitate the option of MBSR for appropriate patients with chronic pain.
- Our results may be limited by heterogeneity from smaller trials.

**Trials registration number:** PROSPERO  
CRD42014015568.

## INTRODUCTION

### Chronic non-cancer pain and its treatment

Chronic non-cancer pain (CNCP) refers to pain of non-malignant aetiology that lasts for more than 3 months. It is a condition commonly seen in any population which is often clinically challenging to manage. Worldwide prevalence of CNCP ranges from 10.1% to 55.2%,<sup>1</sup> and in the USA, CNCP affects more than 100 million people, entailing combined direct and indirect costs of US\$635 billion annually.<sup>2</sup> In Canada, it has been estimated that one in five Canadians are afflicted with CNCP.<sup>3 4</sup> A questionnaire study reported CNCP prevalence of 55–72% among the East London dwellers.<sup>5</sup> Using a Human Development Index of 0.9 as the watershed between developed ( $\geq 0.9$ ) and developing countries ( $\leq 0.9$ ), a

recent systematic review of studies showed that CNCP is more prevalent in developing countries.<sup>6</sup> The whole list of CNCP diagnoses runs long, with the leading four being osteoarthritis, low back pain, headaches and neuropathic pain.<sup>2</sup> The latest consensus describes CNCP as a neuro-signature which is automatically generated within the central nervous system, at an intensity depending on net interactions between the somatosensory, cognitive and affective domains.<sup>7 8</sup> Opioids have widely been used by clinicians to treat CNCP, despite divergent opinions and cautionary notes on their efficacies and indications.<sup>2</sup> An initial Cochrane review in 2007 did not support evidence of using opioids for chronic low back pain.<sup>9</sup> However, such opinion was reversed by Cochrane in 2013, showing short-term efficacy of opioids for chronic low back pain.<sup>10 11</sup> Thus said, patients with CNCP are often not effectively treated, with up to 40% having uncontrolled pain.<sup>4</sup> Effective management for CNCP should extend the classic thinking of the analgesic ladder described by WHO<sup>12</sup> to a broader analgesic platform,<sup>8</sup> incorporating non-pharmacological treatment options, such as physiotherapy, acupuncture, chiropractic, mindfulness-based therapy, cognitive behaviour therapy, relaxation, yoga and other mind-body therapies. Recent systematic reviews found favourable evidence of non-pharmacological modalities for CNCP in both general<sup>13</sup> and elder populations.<sup>14</sup> Among these options, mindfulness-based stress reduction (MBSR) therapy, a form of mind-body therapy, has been widely advocated for patients with CNCP.

### Description of the intervention

First described by Kabat-Zinn<sup>15</sup> as an out-patient programme for patients with various conditions of chronic pain that could not be treated effectively within hospital, MBSR therapy combines meditation, body-awareness and yoga to enhance the individual's ability to self-regulate and hence cope with the pain experience. The two kernels of MBSR are mindfulness and meditation. Kabat-Zinn defined mindfulness as 'intentional, non-judgmental and accepting awareness and focus of oneself', and meditation as 'disciplinary self-regulation of attention from moment to moment'.<sup>15</sup> Combined, mindfulness meditation is a practice with ancient roots in Theravada Buddhism (known as *sattipatana vipassana*) and Mahayana Buddhism and yoga.<sup>15</sup> The original programme described by Kabat-Zinn consists of 10 weekly lessons each lasting 2 h, where three practices will be taught: (1) total body scan (sweeping) from head to toes, where the individuals lie supine and regulate their attention to body sensation and relaxed breathing; (2) mindfulness of sensation and breathing where the individuals sit in a chair and focus intentionally and non-judgmentally on themselves and (3) Hatha yoga postures where the individuals meditate to be detached and observe their inner emotions and thinking processes such that if they drift, the individuals will direct attention to themselves from moment to moment. In the first

4 weeks, sweeping and mindfulness will be taught with supplementary audio-cassette tape instructions for daily practices. In the next 4 weeks, Hatha yoga will be added to intercalate with sweeping, to be practised daily aided by audio-cassette tape instructions. From weeks 9–10, individuals will be allowed to practise any routines previously taught for 30–45 min a day. Compared with controls, Kabat-Zinn found that individuals who went through the MBSR programme had significant reduction in pain, negative body image, mood disturbance, analgesics requirement with an increase in self-esteem and physical activity levels. Such improvements were sustained through 15 months of post-treatment.<sup>16</sup> Soon after, MBSR evolved to be a main-stream patient-centred curriculum hosted by the University of Massachusetts, consisting of an 8-week programme with a weekly 2½ h class and one all-day class, totally 31h of instruction. Similar to the original programme that Kabat-Zinn used in 1982, the content comprises instructions on mindfulness, meditation and yoga techniques supplemented by audio-visual guidance and home practice.<sup>17</sup> This format of MBSR is often adopted by clinical studies and trials as the standard regime, referred as the Kabat-Zinn protocol. It also becomes popular, globally, that interested people can be trained to become certified MBSR instructors in over 30 countries.<sup>18</sup> Not surprisingly, the upsurge of MBSR practice aroused intense research interests and led to a 10-fold jump in annual publications in this topic from year 2003 to 2012.<sup>18</sup>

### How the intervention might work

#### Psychological theory

The current belief states that MBSR offers benefits by regulating attention to present moment awareness of the body and emotions, acknowledging their changes and shifts in an observant and non-judgemental manner. This results in a state of equanimity in the body and mind which will alleviate and even remove all pain and physical sufferings in the mind-body continuum.<sup>15 16 19</sup> The net outcomes include direct reduction of stress and improvement of mood, hence translating to better tolerance of pain and increased exercise tolerance, hence enhanced quality of life.<sup>16</sup>

#### Biological markers

Scientists have reported biological markers as surrogate measures for the therapeutic effects of MBSR. Physiologically, serum cortisol level is a quantifiable measure of stress. In two separate studies, Carlson *et al.*<sup>20 21</sup> demonstrated significant reduction of salivary cortisol concentration after participation in the MBSR programme with matching improvement in symptoms of stress and sleep patterns. Another hypothesis states that MBSR exerts its positive effects via modulation of the immune system. However, results from studies have not been conclusive.<sup>22 23</sup> Other immune and proinflammatory markers being implicated for the therapeutic mechanisms of MBSR-included serum natural killer

cells,<sup>24</sup> C reactive protein<sup>25</sup> and gene expression of the NF- $\kappa$ B (nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells).<sup>25</sup>

### fMRI neuroimaging

Functional MRI (fMRI) is a real-time neuroimaging technique which detects changes of oxygenation within neuronal tissues as a result of neural activities, hence identifying neuroanatomical substrates that were active within the defined time. Using fMRI, MBSR has been shown to alter the functional connectivity between areas of the brain that are known to control attentional focus and sensory processing.<sup>26</sup> MBSR can also alleviate negative emotions aroused by unpleasant stimuli,<sup>27</sup> or, directly inhibit the brain areas that respond to aversive stimuli.<sup>28</sup> One study even showed that a standard 8 weeks MBSR therapy improved mild cognitive impairment in patients with Alzheimer's disease.<sup>29</sup>

### EEG and magnetoencephalography

In parallel with fMRI findings, studies have shown MBSR leads to recognised patterns of change in EEG activities. Again, there is lack of consensus.<sup>30–32</sup> Using more advanced technology of magnetoencephalography (MEG), similar patterns of signal enhancement have been found after MBSR practice, in particular areas of the brain that modulate attention and somatosensory reception of the body.<sup>33 34</sup> However, MEG recordings are always challenged by issues of sensitivities and stray signals, and positive changes in patterns may not be localising enough for meaningful neuro-anatomical correlation.

### Why is it important to do this review?

Two systematic reviews had been published which looked at use of MBSR for CNCP.<sup>35 36</sup> Analysis of the clinical trials that were included showed a certain level of heterogeneity in terms of the actual intervention used, the conditions of chronic pain, and the outcome measures. In particular, the inclusion of fibromyalgia and chronic fatigue syndrome under the category of chronic pain will inevitably confound the results due to possible somatisation variables. Also, a number of relevant controlled clinical trials have been published since 2011 which were not included in the reviews by Teixeira<sup>35</sup> and Veehof *et al.*<sup>36</sup> This forms the basis of this proposed systematic review and meta-analysis (table 1).

## OBJECTIVES

The primary objective of this systematic review is to provide an updated evaluation of the efficacy of MBSR as the sole intervention for non-somatisation types of CNCP.

## METHODS AND ANALYSES

A systematic review and meta-analysis will be performed according to the format specified in the Cochrane

Handbook for Systematic Reviews of Intervention.<sup>37</sup> The logistics and reporting will conform to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statements.<sup>38</sup> Quantitative data derived from the randomised trials as published in the included studies will be systematically reviewed and meta-analysed.

## Criteria for considering studies for review

### Types of studies

This review will only include fully published randomised controlled trials (RCTs) (either in full scale or as pilot, irrespective of blinding status) that look at the effects of MBSR in the treatment of CNCP. MBSR must be given as the sole intervention, lasting at least six sessions, delivered either face-to-face or by online mode. The control group can be either passive (ie, watchful waitlist) or active (receiving other standard care or pain management). Quasi-RCTs will not be included.

### Types of participants

Participants of either gender, aged 16 years or above, having a form of chronic pain (specified or not) of more than 3 months' duration, which is not related to a cancer or somatisation diagnosis will be eligible. Patients with known psychiatric disorders, taking medications or undergoing active interventions for chronic pain will be excluded.

### Types of interventions

MBSR must be given as the sole intervention lasting at least six sessions, delivered either face-to-face or by online mode. The control group can be either passive (ie, watchful waitlist) or active (receiving other standard care or pain management).

### Types of outcome measures

The following outcome measures will be evaluated basing them on reported data analysis accrued from individuals in each included trial:

- ▶ Primary outcome
  - Pain scores either as visual analogue scale or numeric pain score
- ▶ Secondary outcome
  1. General well-being and quality of life—SF-36, SF-12;
  2. Disability scores –Pain Catastrophizing Scale, Roland Morris Disability Questionnaire.

## Search methods and strategies

### Electronic searches

Two reviewers (LL and HH) will perform an electronic search using the following databases from the OvidSP portal of the Queen's University:

- ▶ MEDLINE (1946 to 9 November 2104);
- ▶ EMBASE Classic+EMBASE (1947 to 9 November 2014);
- ▶ PsychINFO (1967 to 9 November 2014);

**Table 1** Characteristics of included studies included by the systematic reviews of Veehof *et al*<sup>36</sup> and Teixeira<sup>35</sup>

Review	Number of studies included	Pain conditions (number of studies)	Interventions used (number of studies)	Outcome measures (number of studies)
Veehof <i>et al</i> <sup>36</sup>	22: 9 RCT+13 CT	10 Chronic pain 4 Fibromyalgia 4 Chronic fatigue Syndrome 2 Rheumatoid arthritis 1 Chronic headache 1 Whiplash injury	14 MBSR 7 ACT 1 MBSR+Qigong	15 use a pain score with depression/QoL scores 7 use depression/QoL scores only
Teixeira <sup>35</sup>	10: 4 RCT+6 CT	7 Chronic pain 2 Fibromyalgia 1 chronic headache	7 MBSR 1 MBSR+aromatherapy 2 meditation	9 use a pain score with depression/QoL scores 1 use depression/QoL scores only

ACT, acceptance and commitment therapy; CT, controlled trial; MBSR, mindfulness-based stress reduction; QoL, quality of life; RCT, randomised controlled trial.

- ▶ Cochrane Central Register of Controlled Trials (up to and including October 2014).

The following MeSH terms will be used: 'randomised', 'randomized', 'controlled trials', 'chronic pain', 'mindfulness' and 'mindfulness-based stress reduction'. After selecting the four databases, sequential searches using each MeSH term as a keyword will be made, which will then be concatenated with BOOLEAN operators as a final search string, as follows:

((('Mindfulness-based stress reduction') OR 'mindfulness') AND ((randomised) OR randomized)) AND (('chronic pain') AND 'controlled trial').

Search for earlier records will not be attempted, as mindfulness-based interventions did not come into existence before 1946. Owing to different workplace locations of LL and HH, non-identical computers will be employed but identical search protocols will be used via the same gateway from the URL link on the website of Queen's Health and Life Sciences Database Services.<sup>39</sup>

#### Other searches

Results from this initial search will be supplemented by additional records from bibliography lists of relevant and index review papers as mentioned in the previous sections. Grey literature will also be searched via the 'GREY MATTERS' checklists from the Canadian Agency for Drugs and Technologies in Health (CADTH).<sup>40</sup> If deemed appropriate, conference proceedings and correspondence with experts in the field will also be considered.

#### Logistics and output

Using the PRISMA flow diagram for reporting systematic reviews and meta-analyses (see online supplementary appendix A),<sup>38</sup> all pooled records will be de-duplicated with additional filters added. Non-English studies and records without full texts will be excluded, so also studies that are irrelevant to the context. The two reviewers will compare their search results, and if

mutual concordance is within 95%, the records will be accepted with the contested records included.

### Data collection and analysis

#### Selection of studies

Basing on the retrieved titles and abstracts, three reviewers (LL, HH and MM) will screen the studies according to the inclusion and exclusion criteria as listed above. If in doubt, the full text of the study will be retrieved either via online or through the help of Queen's University Librarian at the Bracken Library. All reviewers will meet at least twice to discuss and compare their verdicts. If in doubt, full texts of the articles will be retrieved for more detailed examination. Discrepancies and inconsistencies will be discussed and reconciled. An inter-rater concordance of 95% will be targeted before moving onto the next stage. Any contested record(s) will not be included for data extraction.

#### Data extraction and assessment for relevance

After finalising the studies for meta-analyses, two reviewers (LL and HH) will perform data extraction for each study using two tools: (1) the Cochrane Data Collection Form (RCTs only)<sup>41</sup> and (2) the Review Manager (RevMan) software V.5.3.5.<sup>42</sup> Data will be entered as per the following domains:

- ▶ For methods, the design of study (randomised or non-randomised, pilot or full);
- ▶ For participants, the total number with basic characteristics, pain conditions, their allocation groups and sizes with randomisation protocol (if appropriate);
- ▶ For interventions, details of intervention in nature and duration versus control;
- ▶ For outcomes, the drop-out versus completion rate, time point(s) of measurement, the tool(s) used and modality of final analysis (per-protocol vs intention-to-treat).

Where there is more than one measure outcome for each study, data will be entered separately for each outcome to enable individual analysis. In this meta-analysis, the default data type will be continuous data expressed in means and SD for participants in the intervention versus control group. Data in other forms will be converted accordingly to enable pooled analysis. Two other reviewers (JK and MM) will revise the accuracy of the extracted data, and any disagreement and discrepancies will again be resolved by consensus meetings and additional consultation with our in-house statistician.

### Risks of bias assessment

The methodological vigour and quality of each study will be evaluated with the Cochrane Risk of Bias Assessment tool<sup>37 43</sup> which is an integral part of the Cochrane Data Extraction Form and the RevMan programme. Here six domains of bias (selection, performance, detection, attrition, reporting and other) will be assessed, each to be graded as either 'low-risk', 'unclear-risk' or 'high-risk' with juxtaposed commentary space to support such rating.<sup>43</sup>

### Data analysis and synthesis

#### Unit of analysis

Each individual in every included trial as randomised to any arm will be counted only once as a single unit. Where possible, the same measurement time point will be used across different studies. If not possible, the nearest time point data will be adopted.

#### Measurement of treatment effect

The RevMan 5.3.5 programme will be used as the principal tool for meta-analysis. The random effects model will be chosen instead of the fixed effects model, in view of the potential yet uncontrollable heterogeneity of diagnoses that were categorised as 'chronic pain' in the included studies. For each measure of outcome, continuous data as expressed in means from included studies will be extracted and analysed, generating a standardised mean difference (SMD) as the effect size with 95% CIs. The Hedges *g* statistic, as described by Hedges and Olkins,<sup>44</sup> is the default formulation adopted by the RevMan programme to derive the SMD.<sup>45</sup> Where appropriate, the weighted mean difference will also be quoted for analysis.

#### Data integrity and dealing with missing data

Two reviewers (MM and JK) will be responsible for error checking of all text and quantitative data as entered by the other two reviewers (LL and HH). In case of missing, incomplete or equivocal data, efforts will be made to contact the authors of published trials for clarifications and advice.

### Assessment of heterogeneity

To assess heterogeneity of studies, the  $\tau^2$ ,  $\chi^2$  and  $I^2$  statistics will be reported in parallel with the SMDs. The  $I^2$  statistic will be chosen as the reference measure for comparison. By common convention, a value of  $\leq 25\%$  indicates low heterogeneity;  $I^2 \leq 50\%$  indicates moderate heterogeneity, and  $I^2 \geq 75\%$  indicates high heterogeneity.<sup>46 47</sup> Where necessary, Forest plots and heterogeneity funnel plots will be generated for visual presentation. Funnel plots are useful as a quick screen for publication biases, which are often found in smaller studies that report significant effects in their outcomes. Thus said, funnel plots, per se, are not specific for publication biases.<sup>48</sup>

### Subgroup analysis

No subgroup analysis is planned for our study. Studies reporting more than one outcome will be meta-analysed as per the same measure outcome. Any outcome shared by two or less studies will not be included in the final results and discussion.

### Sensitivity analysis

Where appropriate, a rerun meta-analysis will be performed with the fixed effects models to explore the impact of smaller trials. Sensitivity analysis will also be scheduled subject to advice from a statistician.

### Management of research materials and progress monitoring

All data and research materials in this study will be managed electronically, and data will be saved and password encrypted. To ensure accessibility across geographic domains, files will be uploaded to a trusted cloud-based platform. For data security, backup of electronic files will be made frequently onto duplicate sets of USB flash drives that will be kept by LL and one other reviewer in rotation. Correspondence for update and exchange of materials will be made electronically via encrypted email. Face-to-face meetings will be scheduled periodically once every 2 weeks for reporting and progress monitoring. Where physical presence is not possible, over-the-network meetings will be conducted.

### Ethics, knowledge dissemination and impact of study

No ethics approval will be necessary for this meta-analysis. This study aims to provide a more updated and critical evaluation of the effects and efficacy of MBSR as a single intervention for chronic pain conditions that are not associated with somatising or cancer elements. On completion of the study, results will be disseminated to fellow researchers and medical professionals via peer-reviewed publications and international conferences. The reviewers anticipate that this study will provide better evidence-based guidance for healthcare stakeholders and policy setters in deciding whether MBSR is a cost-effective therapy for this category of chronic pain.

**Contributors** LL initiated and conceptualised the research objectives and questions, completed the first round of electronic search, selection of publications and assessment of their eligibility and quality. The other three reviewers (HH, MM and JK) started collaboration with LL to revise the completed tasks and to pursue subsequent processes. LL drafted the manuscript for this protocol, receiving critical comments from the other reviewers.

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