MEDITATION FOR ASTHMA: SYSTEMATIC REVIEW AND META-ANALYSIS

Running title: Meditation for Asthma

Key words: meditation, mindfulness, asthma, randomised controlled trials, quality of life, lung function
ABSTRACT

Objective: To conduct a comprehensive review and meta-analysis of the effectiveness of meditation on a variety of asthma outcomes.

Methods: We searched MEDLINE, EMBASE, CINAHL, PsycINFO and AMED in June 2016 to identify randomised controlled trials (RCTs) investigating the effectiveness of meditation in adults with asthma. No restriction was put on language or year of publication. Study quality was assessed using The Cochrane Risk of Bias Assessment Tool. Meta-analysis was carried out using RevMan 5.3.

Results: Four RCTS involving 201 patients met the inclusion criteria. Quality of studies was inconsistent with only one study reporting adequate allocation concealment. Disease-specific quality of life was assessed in two trials; a pooled result involving 62 intervention and 65 control participants indicated a significant improvement in quality of life in the meditation group compared to the control group (SMD 0.40, 95% CI 0.05 to 0.76). A pooled result from all four studies indicated the uncertain effect of meditation in forced expiratory volume in one second (FEV₁) (SMD -0.67, 95% CI -2.17 to 0.82). Results from the individual trials suggest that meditation may be helpful in reducing perceived stress and the use of short-term rescue medication.

Conclusion: Our review suggests that there is some evidence that meditation is beneficial in improving quality of life in asthma patients. As two out of four studies in our review were of poor quality, further trials with better methodological quality are needed to support or refute this finding.
BACKGROUND: Asthma is a chronic respiratory disease that affects 334 million people worldwide. The disease is the 14th most important disorder in terms of the extent and duration of disability globally (1). Asthma imposes significant economic burden with an estimated annual cost of $56 billion in the USA (2007 estimates), and €19.3 billion among Europeans aged from 15 to 64 years (2011 estimates) (1). In Asian-Pacific countries like Vietnam and Hong Kong, the sum of direct and indirect costs of asthma per person per year was estimated to be $184 and $1,189 respectively (in 2000 US dollars) (1). Despite a range of pharmacological treatments for asthma, many patients still experience residual and troublesome symptoms that adversely affect their quality of life. Therefore, patients with asthma often seek complementary treatment strategies that may enhance their pharmacological asthma treatment regimens.

Complementary and Alternative Medicine (CAM) is widely used by patients with asthma, the prevalence rates ranging from 4% to 79% (2). Studies examining the effectiveness of CAM as a treatment modality for asthma seem to adopt the approach of using CAM techniques as an adjunct to conventional medication, rather than an alternative to it (3, 4). Evidence suggests that concern about the adverse effects of orthodox asthma treatments and desire for greater self-care with a more holistic approach are the main reasons behind CAM use (5) (6) (7). The extent of CAM use has been acknowledged in BTS guidelines which recommend that health care practitioners should be aware of the frequent use of CAM amongst patients with asthma and should enquire about its use (8). This may assist health care providers to engage actively with their patient about overall asthma management, thus leading to better health outcomes. The increasing popularity of CAM use in asthma
necessitates the investigation of effectiveness and safety of such therapies in order to identify and implement evidence-based CAM approaches in the management of asthma.

Stress is linked with asthma, both as a precursor or as an outcome (9-11). Recent studies have reported strong associations between stress and asthma incidence, hospitalisation and the use of asthma medication (10, 12). Therefore, interventions aimed at reducing stress may have a positive impact on patients' quality of life and disease course. Various CAM techniques such as relaxation and yoga have been employed to address stress and anxiety in patients with asthma, however the findings from these studies are inconclusive (13, 14).

Meditation is a popular adjunct to traditional therapies. The result from a national survey published in 2010 shows that meditation is among the top ten most commonly used CAM practices in England (15). Meditation is defined as an “intentional self-regulation of attention from moment to moment” (16). The practice is broadly classified into two major groups; concentration meditation (restricting attention to a single point or object) and mindfulness meditation (observing sensations, thoughts or emotions without making judgements, although this can also involve focusing on the breath) (17). Research has demonstrated that meditation can have a positive effect on health and can alter human psychological states and physiological states such as serum cortisol levels, blood pressure, pulse rate and respiratory rate, vital capacity and body temperature (18, 19). The role of meditation has been investigated for a wide variety of chronic disease conditions including fibromyalgia, cancer and depression (20-22). However, the role of meditation in asthma remains critically unevaluated and we are unaware of any reviews of existing quantitative assessments. This study fills this gap with a comprehensive review and meta-analysis of
the effectiveness of meditation on a variety of asthma outcomes, including quality of life, pulmonary function, asthma exacerbations, and psychological well-being.

**METHODS:** The protocol for this systematic review was registered in PROSPERO 2016:CRD42016038377. The review was conducted and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (http://www.prisma-statement.org/).

**Information sources:** We conducted an electronic search to retrieve articles that have investigated the effectiveness of meditation on the management of asthma. We searched the following electronic bibliographic databases: MEDLINE, EMBASE, CINAHL, PsycINFO and AMED. The databases were searched between June and Sept 2016. All references in the identified articles were screened for relevant articles.

**Eligibility criteria:** Studies were included if (i) they were a randomised controlled trial (RCT) involving meditation; (ii) comparison was made with sham therapy, active comparator treatment, waiting-list control or usual care; (iii) the study involved adults (≥18 years) with asthma. No restriction was put on language or year of publication. Studies of Mindfulness Based Stress Reduction (MBSR) were included as although they include three forms of practice including yoga, all are taught as different aspects of mindfulness. In contrast, studies where meditation was a minor component of other practitioner-based therapies (including yoga) without the same emphasis on mindfulness were excluded from the review.

**Search:** Three search themes were used to interrogate electronic databases: (i) identification of the disease i.e. asthma, (ii) identification of CAM therapy i.e. meditation,
and (iii) identification of relevant study design, i.e. RCTs. These terms were then combined using the Boolean operator AND. The search was based on the Cochrane-suggested terminology for asthma, meditation and RCT.

**Study selection:** Literature search was carried out by two independent researchers (CG and RD). Three independent reviewers screened the titles of the articles, and irrelevant and duplicate articles were excluded (PP, RD and CG). Abstracts of the relevant articles were further screened applying the eligibility criteria and full articles were retrieved. We also searched the rgraphies of all selected relevant articles to identify additional relevant publications. Any discrepancies relating to eligibility were resolved by discussion with a fourth reviewer (HS) to achieve consensus.

**Data extraction and items:** A descriptive summary table was produced to summarise the eligible studies included in the review. The following information was extracted from the selected studies: country and publication year, study setting, patient characteristics (age, sex), asthma severity, details of intervention and control, duration of treatment and length of follow-up, outcome measures studied, and data on the statistical significance of change of outcome measure in the meditation group in relation to control group.

**Outcome Measures:** The primary outcome was asthma-related quality of life. Secondary outcomes of interest were lung function (forced expiratory volume in 1 sec, forced vital capacity, peak expiratory flow), asthma symptoms, asthma exacerbation, frequency of hospitalisation, use of asthma medication, psychological well-being and safety of meditation (drop out because of adverse events or serious adverse events).
Assessment of risk of bias in the studies: Two reviewers (PP and CJ) were involved in the risk of bias assessment. Risk of bias was assessed using The Cochrane Collaboration Tool (Table 8.5.a in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.0.0). The tool contains six domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other sources of bias). A judgement was made regarding the risk of bias for each of these domains using three categories ‘low’, ‘high’ and ‘unclear’ if the study details were insufficient.

Statistical Analysis: We performed a preliminary narrative synthesis of the data. Depending on the heterogeneity of the studies, we performed either a fixed-effect or a random effect meta-analysis. Heterogeneity of the trials was assessed through visual inspection of forest plots and calculation of the $I^2$ statistic using a 50% limit to indicate substantial heterogeneity (23). End point scores were expressed as standardised mean differences (SMDs) with associated 95% confidence intervals (CIs). We performed the meta-analysis using RevMan 5 software (24). We intended to assess the publication bias using funnel plot, however, this was not carried out as there were less than 10 studies included in our meta-analysis (25).

RESULTS

A total of 4193 references were initially identified from the computerized search. After removing 362 duplicates, titles of the remaining 3831 articles were screened, 318 abstracts were retrieved for further scrutiny, and 28 articles read in full. The four studies meeting the inclusion criteria were included in this review (Figure 1). The interrater reliability for abstract
screening was moderate (kappa=0.7) between the reviewers (PP and RD). Both reviewers had agreement on the final four full text articles that were included in this review.

**Characteristics:** The study characteristics of the studies are described in Table 1. Two studies were conducted in the USA (26, 27), one in Australia (28) and one in India (29). Three studies were parallel group RCTs and one was a cross-over RCT. All of the studies had one intervention group and one control group. Trial duration varied from 8 weeks to 16 weeks and follow-up period ranged from 5 months to 12 months.

A total of 196 participants were involved in the analysis of studies included in this review. The numbers of eligible and randomly assigned participants and the details of participants dropout and adherence were detailed in only two studies (26) (28). The average age of participants ranged from 29 to 53 years. One study included equal numbers of male and female participants (29). The remaining studies had a higher proportion of female participants. The interventions varied greatly between the studies. The first study used a Mindfulness Based Stress Reduction (MBSR) programme as an intervention (26), the second study used Sahaja yoga meditation, the third used transcendental meditation and meditation was used as a control intervention in the fourth study which was evaluating breathing exercises [25].

**Effect of Interventions:** We entered the relevant data and created forest plots. However, we were only able to pool the data for asthma-related quality of life, FEV$_1$, and PEF. We could not pool data for other outcomes because of divergent outcome measurements and insufficient reporting of data. Results are presented below for each outcome, starting with the primary outcome of lung function.
**Asthma Quality of Life:** The impact of meditation on disease-specific quality of life was assessed in two trials. The trial by Pbert *et al* (26) used The Juniper Asthma Specific Quality of Life Questionnaire (AQLQ-J) comprising 32 items (30) and the trial by Manocha (28) used the Sydney Asthma Specific Quality of Life Questionnaire (AQLQ-S) comprising 20 items. A pooled result involving 62 intervention and 65 control participants indicated a significant improvement in quality of life in the meditation group compared to the control group at the end of the study period (SMD 0.40, 95% CI 0.05 to 0.76) (Figure 2).

**Lung function:** All four studies measured FEV₁ and PEF. A pooled analysis of the heterogeneous data ($I^2 = 95\%$; $P$ value <0.001), including a total of 96 intervention and 100 control participants, indicated no statistically significant differences in FEV₁ between the meditation group and the control group at the end of the study period (SMD -0.67, 95% CI -2.17 to 0.82) (Figure 3). Similarly, a pooled result from the same studies indicated that meditation results in no significant improvement in PEF in participants with asthma (SMD -1.23, 95% CI -3.53 to 1.07) (Figure 4).

**Other Outcomes:** Asthma symptoms were evaluated in two studies (27, 29), however, the data could not be extracted from the first study. The second study which used Pranayama breathing exercises as an active intervention and meditation as a control, reported significant improvement in FEV₁% predicted (88% vs 75%, $p<0.001$) and number of participants reporting symptoms (10% vs 72%, $p<0.01$) in the relaxation group compared to the meditation group. Asthma control, perceived stress, and medication use were measured in only one study (26). The study found significant benefit from meditation in perceived stress (Perceived Stress Scale score at 12 months 13 vs 16; $p<0.001$) and medication use
(short-term rescue in medication use 2.39 vs 2.49; p < 0.001) but no significant improvements were reported in asthma control.

Quality of the studies: The quality of the studies varied greatly: one study was rated as low risk of bias in six out of seven domains (28), another was rated as high risk for all domains (27), the third was rated as low risk for four domains and unclear for allocation concealment and blinding (26), the fourth was rated as high risk for four out of seven domains (29) (Table 2).

Sensitivity analysis: The two low quality studies (27, 29) did not assess quality of life. We conducted a sensitivity analysis for other outcomes (FEV1 and PEF) excluding the low quality studies, however, the results did not differ (specifically there was no significant overall improvement in FEV1 and PEF observed). The sensitivity analysis also showed that these two studies contributed to substantial heterogeneity for the lung function outcomes. The heterogeneity for FEV1 was reduced from 95% to 11% after the exclusion of study by Saxena et al (29) and to 0% when both studies were excluded. When same approach was used for PEF, I^2 value for PEF was reduced from 97% to 83% and then to 0%.

DISCUSSION: This review found some evidence that meditation has beneficial effects on improving quality of life in patients with asthma but not on lung function. Results from the individual trials suggest that meditation may be helpful in reducing perceived stress and the use of short-term rescue medication. Although adherence to meditation was reported in two trials (26) (28), none of the trials assessed the safety of the intervention. The independence of quality of life improvement from lung function is consistent with the other CAM reviews on asthma. Meditation is used as a common component of yoga, and a recently published
Cochrane review on the effectiveness of yoga on asthma also found moderate-quality evidence that yoga may contribute to small improvements in quality of life and symptoms, but not on lung function (31). The findings from our review, however, contradicts with a recently published review on mindfulness in respiratory disease (32), which did not find any impact of mindfulness on asthma-related quality of life. The review was markedly limited by the inclusion of heterogeneous patient groups such as COPD, asthma and other critical illnesses requiring mechanical ventilation.

The exact mechanism on how meditation may work in asthma is unclear. It has been reported that meditation may be beneficial in the control and feedback of respiratory muscles which come into play during asthma attacks (33). The practice of meditation may contribute to a sense of relaxation and a positive mood, helping users to achieve a state of mental silence, which is considered to be an innately therapeutic process in managing chronic disease like asthma (34). Studies exploring the effects of meditation on the autonomous nervous system have reported increased parasympathetic and reduced sympathetic nerve activity with increase in overall heart rate variability and cardiorespiratory synchronisation (35) (36). This can be supported from the findings of two studies included in this review; one reported substantial reduction in perceived stress (26) and the other reported improvement in mood after the practice of meditation (28).

This is the first review to assess the effectiveness of meditation in asthma. It summarises data derived from the RCTs with meta-analysis of their results. We conducted a comprehensive literature search without any restriction on date or language. We used a pre-specified protocol for trial selection and data extraction however, it must be acknowledged that some unpublished trials may have been missed as we did not perform the search of grey literature. Another limitation of this review is the quality of the included studies. Out of four studies, two were of low quality, one was moderate quality and only one
was of high quality reporting adequate allocation concealment. Previous reviews have reported that lower quality RCTs tend to report a larger effect than high-quality RCTs (37, 38). As inadequate allocation concealment has been empirically demonstrated to be the most important source of bias in RCTs, the findings of our review must be interpreted cautiously. The meta-analysis for lung function outcomes (FEV₁ and PEF) showed substantial heterogeneity due to the inclusion of low quality studies. However, the sensitivity analysis showed that although heterogeneity was reduced after the exclusion of poor quality studies, there was no change in the direction or size of effect for lung function outcomes. Many outcomes were measured in one study only; limiting the data that could be pooled. Also the type of intervention, outcome measure, outcome measurement tool, and study duration varied across trials. The aim of the meditative practice is to establish a lifelong habit of the meditation, however, three out of four trials failed to assess the long-term effectiveness of the practice. Our review did not aim to assess the cost-effectiveness of the intervention, but none of the studies investigated whether these interventions were cost-effective compared to other common interventions in asthma. Exploring cost-effectiveness of meditation interventions in a future trial would enable assessment of the financial consequences of implementing them into routine clinical care.

In summary, there is a paucity of good quality studies examining the role of meditation in asthma. Based on the results of the RCTs included in this review, there is some evidence that meditation is beneficial in improving quality of life in asthma patients. As only four studies were eligible and two were of poor quality, further trials with better methodological quality are needed to support or refute this finding. Variation in measurement tools, divergent outcomes and selective reporting in the studies suggest that there is a need to standardise outcome measurement tools in asthma. Future trials would benefit from
stratifying participants by asthma severity and assessing safety of the intervention to allow patients and clinicians to make an informed decision regarding their management plan.

REFERENCES:


<table>
<thead>
<tr>
<th>Reference, country</th>
<th>Male/Female</th>
<th>Age in years</th>
<th>Asthma Severity/control</th>
<th>Study setting</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>Treatment duration, follow-up</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Pbert et al 2012, USA (26)</td>
<td>27/56</td>
<td>Mean age:53</td>
<td>Patients with mild, moderate or severe asthma</td>
<td>UMass Memorial Health care, Worcester, Massachusetts</td>
<td>MBSR-weekly 2.5 hour sessions and an all-day 6 hour session in the 6th week. Participants provided with 2 CDs containing guided instruction for mindfulness exercise to practice for 30 minutes, 6 days/week (n=42)</td>
<td>Healthy Living Course-lecture and discussion of topic related to self-care. Behaviour homework assigned in consistent with MBSR programme (n=41)</td>
<td>8 weeks, follow up at 12 months</td>
<td>Difference (+): AQOL perceived stress, medication use No difference (-): FEV1, PEF, asthma control</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>Mean (SD)</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcome Measures</td>
<td>Follow-Up</td>
<td>Other Outcomes</td>
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<td>Saxena 2009, India (29)</td>
<td>India</td>
<td>25/25</td>
<td>29 (7.5)</td>
<td>Patients with bronchial asthma, severity not reported</td>
<td>University Hospital, Ajmar, India</td>
<td>Breathing exercises/pranayama -20 minutes twice daily (n=25)</td>
<td>Meditation-20 minutes for 12 weeks (n=25)</td>
<td>12 weeks</td>
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<td>Manocha 2002, Australia (28)</td>
<td>Australia</td>
<td>21/26</td>
<td>Not reported</td>
<td>Patients with moderate or severe asthma with a asthma score of at least 7 out of 12</td>
<td>Participants encouraged to meditate 10-20 minutes daily, twice a day. Weekly 2 hour session involved meditation, instructional videos, personalised instructions and discussion on improving the relaxation method, group discussion and cognitive behavioural therapy. Participants encouraged to work on relaxation and stress management technique for 10-20 minutes twice daily (n=26)</td>
<td>Relaxation method, group discussion and cognitive behavioural therapy. Participants encouraged to work on relaxation and stress management technique for 10-20 minutes twice daily (n=26)</td>
<td>16 weeks, follow-up at 20 weeks</td>
<td>Difference (+): None, No difference (-): FEV₁, FEV₁/FVC, PEF, AQLQ</td>
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<tr>
<td>Wilson 1975, USA (27)</td>
<td>9/12</td>
<td>Age range 14-57</td>
<td>Patients with stable asthma for at least 1 year</td>
<td>No reported practice</td>
<td>Read the book ‘Science of being’ and ‘Art of living’ by Maharishi Mahesh Yogi (n=11)</td>
<td>3 months, 6 months</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, PEFR, symptoms measured but no inter-group comparison reported</td>
<td>experience of meditation. (n=21)</td>
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Table 2. Risk of bias summary: author’s judgment about each risk of bias item for each included study

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessor</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>Other sources of bias</th>
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<td>Pbert et al 2012 (26)</td>
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<td>Manocha 2002 (28)</td>
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<td>Wilson 1975 (27)</td>
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+ Low risk of bias, - High risk of bias, ? Unclear
Fig 1: Flow chart of article selection process for this review

Fig 2: Forest plot of comparison: Meditation versus Control, outcome: Asthma-related Quality of Life

Fig 3: Forest plot of comparison: Meditation versus Control, outcome: FEV$_1$

Fig 4: Forest plot of comparison: Meditation versus Control, outcome: PEF