



## Research paper

# The effectiveness of adjunct mindfulness-based intervention in treatment of bipolar disorder: A systematic review and meta-analysis



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## ABSTRACT

**Background:** Mindfulness-based interventions (MBIs) have been increasingly used as an adjunctive treatment to pharmacotherapy for a few psychiatric disorders. However, few studies have investigated the efficacy of MBIs in bipolar disorder (BD).

**Methods:** We performed a systematic review and meta-analysis to evaluate the efficacy of MBIs as an adjunctive treatment in BD. Major electronic databases were independently searched by two authors for controlled and uncontrolled studies which examined the effects of MBIs on psychiatric symptoms in subjects with BD. Data from original studies were synthesized by using a random effects model.

**Results:** Twelve trials were eligible for inclusion into current meta-analysis, including three controlled studies (n = 132) and nine uncontrolled studies (n = 142). In within-group analysis, MBIs significantly reduced depressive (7 studies, n = 100, Hedges'  $g = 0.58$ ,  $p < 0.001$ ) and anxiety (4 studies, n = 68, Hedges'  $g = 0.34$ ,  $p = 0.043$ ) symptoms, but not manic symptoms (6 studies, n = 89, Hedges'  $g = 0.09$ ,  $p = 0.488$ ) and cognition (3 studies, n = 43, Hedges'  $g = 0.35$ ,  $p = 0.171$ ), compared to baseline. In between-group analysis (intervention group versus waiting list group, all patients with BD), MBIs did not reduce depressive (3 studies, n = 132, Hedges'  $g = 0.46$ ,  $p = 0.315$ ) or anxiety (3 studies, n = 132, Hedges'  $g = 0.33$ ,  $p = 0.578$ ) symptoms.

**Limitations:** Only three controlled trials compared MBIs to control conditions.

**Conclusions:** Our meta-analysis showed significantly beneficial effects on depressive and anxiety symptoms of BD patients in within-group analysis. However, this significance was not observed in comparison with the control

**Abbreviations:** BAI, Beck anxiety index; BD, bipolar disorder; BDI, Beck depression inventory; CPAS, clinical positive affective scale; DASS, depression anxiety stress scales; DSM-IV, diagnostic and statistical manual of mental disorders, 4th edition; FFMQ, five-facet mindfulness questionnaire; HADS, hospital anxiety and depression scale; HAMD, Hamilton depressive scale; KIMS, Kentucky inventory of mindfulness skills; MAAS, mindful attention awareness scale; MADRS, Montgomery–Åsberg depression rating scale; MBI, mindfulness-based intervention; n/a, not available; Pre-post Tx, comparison of disease severity before and after treatment; STAI, state-trait anxiety inventory; TAU, treatment as usual; Tx, treatment; YMRS, Young mania rating scale

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groups. Further clinical trials are warranted to investigate the differences in the benefits of MBIs between treatment and control subjects.

## 1. Introduction

The global prevalence of bipolar disorder (BD) in primary care is 1.8% (Stubbs et al., 2016), and it is one of the leading causes of disability worldwide (Garland et al., 2016). BD is characterized primarily by recurring affective episodes of depression, (hypo)mania and mixed states. In addition, patients with BD often have impaired psychosocial functions, even when in remission (Garland et al., 2016). Even after drug treatment, up to 48.5% of patients with BD have been reported to experience relapses and/or recurrence of major affective episodes within a 2-year follow-up period (Perlis et al., 2006). Furthermore, even if these patients improve after acute episodes, pervasive depressive symptoms remain (Judd et al., 2003) in addition to the cognitive symptom of emotional regulation disability (Gruber, 2011). Several psychosocial interventions including interpersonal therapy, family therapy, and cognitive-behavioral therapy have been developed as adjunctive therapy to treat BD (Grande et al., 2016). Among these psychosocial interventions, psychoeducation, interpersonal therapy, family therapy, non-mindfulness based cognitive-behavioral therapy, and systematic care have been proven to be effective in preventing relapses, stabilizing episodes, and reducing episode length (Miklowitz, 2008; Miziou et al., 2015; Oud et al., 2016). For example, a recent meta-analysis by Oud et al. reported that individual psychological interventions could reduce the severity of depressive but not manic symptoms (standardized mean difference [SMD] =  $-0.23$ , 95% confidence interval [CI] =  $-0.41$  to  $0.05$ ; SMD =  $-0.05$ , 95% CI =  $-0.35$  to  $0.25$ , respectively). Another study also suggested that these non-medical therapies could help in ameliorating core inter-episode symptoms (Opialla et al., 2015).

Recently, interest has grown in the potential of mindfulness-based interventions (MBIs) to improve outcomes of patients with psychiatric illnesses. MBIs are based on the premise of paying total attention on purpose in the present moment and non-judgmental attention to inner and outer experiences moment by moment (Kabat-Zinn, 1994). MBIs were first developed by Kabat-Zinn as mindfulness-based stress reduction (MBSR) in the 1970s to enhance the stress coping skills of patients with chronic pain (Kabat-Zinn, 1990). Later, MBIs were used as the core of mindfulness-based cognitive therapy (MBCT) by combining elements of MBSR and cognitive therapy in order to prevent relapses/recurrence of unipolar depressive episodes (Teasdale et al., 1995, 2000). For example, a recent meta-analysis which synthesized available evidence from 1329 participants found that MBCT reduced depressive relapse rates within a 60-week follow-up period compared to participants who did not receive MBCT (Kuyken et al., 2016). Another meta-analysis suggested that MBIs could also be effective as an adjunctive treatment for negative symptoms among patients with psychosis (Khoury et al., 2013).

However, relatively few studies have investigated the effect of MBIs on treatment outcomes in patients with BD. Uncontrolled (Biseul et al., 2016; Bos et al., 2014; Crane et al., 2008; Deckersbach et al., 2012; Howells et al., 2014; Miklowitz et al., 2009, 2015; Murray et al., 2015; Perich et al., 2013a; Stange et al., 2011; Weber et al., 2010) and controlled trials (Ives-Deliperi et al., 2013; Perich et al., 2013b; Van Dijk et al., 2013; Williams et al., 2008) have shown that the combination of MBIs with pharmacotherapy and treatment as usual (TAU) can have beneficial effects for patients with BD. Furthermore, a previous functional magnetic resonance imaging study showed the potential involvement and beneficial effects of MBIs in specific neural circuits underlying emotional regulation (Opialla et al., 2015), which is one of the main core inter-episode symptoms in BD (Gruber, 2011). Conversely, other studies have found no significant effect of MBIs on

depressive (Howells et al., 2014; Ives-Deliperi et al., 2013; Perich et al., 2013b; Weber et al., 2010), manic (Deckersbach et al., 2012; Perich et al., 2013b), or anxiety (Howells et al., 2014) symptoms.

These inconsistencies may be due to the small sample size in most studies (Crane et al., 2008; Deckersbach et al., 2012; Miklowitz et al., 2009; Murray et al., 2015; Perich et al., 2013a; Stange et al., 2011; Van Dijk et al., 2013; Williams et al., 2008), lack of standardized outcome measurement, different intervention characteristics (e.g. study duration varying from 3 to 12 weeks of MBCT training), different characteristics of the participants (Bos et al., 2014; Weber et al., 2010; Williams et al., 2008), high attrition rates early in the study (Bos et al., 2014; Murray et al., 2015), and disparate study designs (Bos et al., 2014; Howells et al., 2014; Murray et al., 2015; Van Dijk et al., 2013). In addition, the absence of a comparison treatment control group in many studies makes the findings less robust when considered in isolation (Bos et al., 2014; Crane et al., 2008; Deckersbach et al., 2012; Miklowitz et al., 2009; Murray et al., 2015; Stange et al., 2011; Weber et al., 2010).

Two meta-analyses investigating MBIs in patients with mental disorders have previously been conducted with mixed groups of patients with mood or anxiety disorders (Chiesa and Serretti, 2011; Hofmann et al., 2010). Whilst helpful, the generic focus, the fact that only two trials involving participants with BD were included, and failure to consider core symptoms of BD such as mania (Chiesa and Serretti, 2011), limits the conclusions regarding the efficacy of MBIs in patients with BD. More recently, several uncontrolled clinical trials examined the effectiveness of MBIs in patients with BD (Biseul et al., 2016; Bos et al., 2014; Miklowitz et al., 2015; Murray et al., 2015), however no dedicated systematic review and meta-analysis has investigated the use of MBIs as treatment for BD.

Given these limitations and gaps in the literature, we conducted this comprehensive systematic review and meta-analysis to investigate the role of MBIs as an adjunctive therapy for patients with BD.

## 2. Method and materials

The current systematic review and meta-analysis was conducted in line with the PRISMA guidelines (Liberati et al., 2009) (Supplement Table 1 and Supplement Fig. 1).

### 2.1. Eligibility criteria

In order to be eligible for inclusion, articles had to meet the following criteria: (1) peer-reviewed original articles investigating the adjunctive effect of MBIs in patients with BD compared to a control group (controlled studies) or without a control group (uncontrolled studies); (2) a diagnosis of BD based on either DSM-IV (Association, 1994) or ICD (Diseases) code (Medicode firm, 1996); (3) used MBIs (including MBSR, MBCT, and other interventions in which mindfulness represented a core component); and (4) articles written in English.

We excluded non-clinical trials articles from the present study (e.g. case series, observational studies). We also excluded studies investigating mixed populations of patients (e.g. both patients with BD and major depression joined), unless the articles provided separated data for those with BD and major depression. In addition, we excluded studies that examined mindfulness as part of another treatment modality as it would have been difficult to differentiate the treatment effect of mindfulness from other components (Khoury et al., 2013). Therefore, we excluded studies on dialectical behavior therapy and acceptance and commitment therapy. We also excluded studies with a short duration (< 3 weeks) and those on self-help interventions such as online MBIs (Murray et al., 2015)

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