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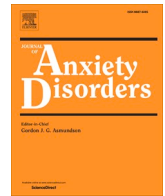
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Mindfulness-based cognitive group therapy for treatment-refractory anxiety disorder: A pragmatic randomized controlled trial

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ABSTRACT

Background: This study aimed: (a) to examine the effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) for patients with a treatment-refractory anxiety disorders compared to Relapse Prevention-Cognitive Behavioral Therapy (CBT-RP); and (b) to explore candidate mediating variables.

Methods: We conducted a pragmatic randomized controlled trial comparing MBCT with CBT-RP in a group format for 136 outpatients with treatment-refractory DSM-IV defined anxiety disorder, who insufficiently responded to first-line psychological treatment.

Results: At post-treatment, the MBCT group showed a significantly larger decrease in self-reported anxiety (Beck Anxiety Inventory), avoidance (Fear Questionnaire), difficulties in emotion regulation (Difficulties in Emotion Regulation Strategies), and worry (Penn State Worry Questionnaire), as well as a significantly larger increase in mindfulness skills (Five Facet Mindfulness Questionnaire). After a 6-month follow-up treatment gains were somewhat diminished. Effects of MBCT on anxiety at post-treatment did not prove to be mediated by mindfulness skills, difficulties in emotion regulation strategies, worry, or rumination (Rumination on Sadness Scales) at mid-treatment.

Conclusions: MBCT seems to be a promising intervention in routine clinical care for persons with an anxiety disorder who insufficiently responded to first-line psychological treatment. Future research in larger samples assessing long-term effects and using intensive longitudinal designs to identify possible working mechanisms is called for.

1. Introduction

With a global prevalence of 7.3% (Baxter, Scott, Vos, & Whiteford, 2013), anxiety disorders are prevalent and cause significant reductions in quality of life (Olatunji, Cisler, & Tolin, 2007). Cognitive Behavioral Therapy (CBT) is widely regarded as the first-line psychological treatment option for anxiety disorders (Bandelow, Michaelis, & Wedekind, 2017). First-line pharmacological treatment options are Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) (Bandelow et al., 2017). Although anxiety disorders have been proven to be treatable conditions and respond to the recommended first-line psychological and pharmacological interventions, only about 60% of patients respond to those treatments to any significant degree. Many patients still have residual anxiety symptoms or remain treatment refractory (Bystritsky, 2006). These high

numbers stress the importance of developing interventions specially tailored for these treatment-refractory patients.

Mindfulness-based cognitive therapy (MBCT), which combines the main principles of CBT with mindfulness-based stress reduction (MBSR) techniques, appears efficacious as a treatment for relapse prevention for those with recurrent depression, particularly those with more pronounced residual symptoms (Kuyken et al., 2016). MBCT focuses on cultivating mindfulness and non-judgmental, present-moment awareness, enabling patients to become more aware of their bodily sensations, thoughts, and feelings (Teasdale et al., 2000).

Because anxiety disorders are characterized by an extensive range of maladaptive somatic and cognitive processes, like hyperarousal, worrying, selective attention, suppression, and experiential avoidance, there is reason to believe that patients with anxiety disorders might also benefit from MBCT (Hofmann & Asmundson, 2008). Mindfulness

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practice may enhance one's ability to maintain a stable focus of attention that is intentional and chosen, as opposed to automatically driven by emotional reactivity. Critically, mindfulness also involves acceptance and non-judgement of our present moment experiences -whether positive or negative- and may result in a more accepting relationship with one's internal cognitive, emotional, and physical experiences, also in times of intense fear or worry.

Several studies showed that mindfulness meditation is superior in reducing anxiety compared to no treatment, minimal treatment, and active control conditions, but not different in outcome from evidence-based treatments (for reviews see: [Goldberg et al., 2018](#); [Hofmann, Sawyer, Witt, & Oh, 2010](#); [Khoury et al., 2013](#)). Studies examining mindfulness-based interventions for DSM-IV/5 anxiety disorders showed short-term effects on clinician- and patient-rated anxiety for these interventions in addition to TAU versus TAU alone and comparable effects on both anxiety outcomes in comparison to CBT ([Haller, Breilmann, Schröter, Dobos, & Cramer, 2021](#)).

Moreover, evidence is accumulating that MBCT may be of value for anxiety disorder patients who continue to report symptoms after first-line pharmacotherapy. In the first study in patients with panic disorder (PD) or generalized anxiety disorder (GAD) who after six months of pharmacotherapy did not achieve remission and continued to report persistent symptoms, MBCT as an adjuvant to the continuation of their pharmacotherapy resulted in more anxiety reduction compared to an anxiety disorder education (ADE) program ([Kim et al., 2009](#)). In a recent RCT in patients with panic/agoraphobia or social anxiety disorder (SAD) of whom the vast majority had already undergone pharmacotherapy without remission, MBCT as an adjunct to continued treatment was more effective in reducing anxiety compared to a waiting list control group ([Ninomiya et al., 2020](#)). Lastly, MBCT as an adjuvant to the continuation of drug treatment was compared with psychoeducation combined with an introductory CBT as active control group in patients with PD or GAD who did not achieve remission following at least eight weeks of adequate pharmacological treatment. Results showed a greater reduction in anxiety and worry severity for MBCT that became particularly evident over the long term ([Gionmi et al., 2021](#)). However, these studies did not include anxiety disorder patients who did not respond to evidence-based first-line psychological anxiety disorder treatments, although CBT is widely regarded as the first-line psychological treatment option for anxiety disorders ([Bandelow et al., 2017](#)).

Many studies have tried to identify mediators (i.e., "an intervening variable that may account statistically for the relationship between an independent variable and dependent variable") and working mechanisms (i.e., "the process that is responsible for change") ([Kazdin, 2007, 2009](#)) underlying the effectiveness of mindfulness-based treatments (for an overview see the systematic reviews of [Gu, Strauss, Bond, & Cavanagh, 2015](#), [van der Velden et al., 2015](#) and [Alsubaie et al., 2017](#)). In a recent systematic review of RCTs of mindfulness-based programs for anxiety, depression, and psychological distress explicitly examining candidate mediators or mechanisms of change using a well-established method of mediation analysis and including a control group, 11 studies were identified ([Maddock & Blair, 2021](#)). In line with previous systematic reviews, most of the included studies only conducted mediation analyses on changes in proposed mediators and outcomes from pre-treatment to post-treatment. However, in order to examine the temporal order of change, which is the first prerequisite for making inferences regarding the causal direction of an association, at least three time points are necessary. Significant concurrent changes determined at two time points only could also be explained by reverse causal direction, reciprocal relationships or a third variable affecting outcome ([Snippe, Nyklíček, Schroevers, & Bos, 2015](#)). Moreover, none of the studies included measures of temporal precedence of changes in the mediator as recommended by [Kazdin \(2007, 2009\)](#). So, there is a dearth of studies examining variables that could mediate the effectiveness of MBCT for different health problems. These studies are needed as active mediating variables may be intensified and refined to improve treatment

effectiveness.

The primary aim of the present study was to investigate the effectiveness of MBCT in reducing anxiety severity in persons who responded insufficiently to first-line CBT compared to Relapse Prevention-Cognitive Behavioral Therapy (CBT-RP), both provided in a group format. As we designed to evaluate the effectiveness of MBCT in a real-life routine clinical care setting in which we tried to control confounding factors as much as possible, the present study can best be characterized as a pragmatic RCT instead of an exploratory trial under optimal conditions. A secondary objective was to explore candidate mediating variables to identify possible mechanisms of change to improve treatment effectiveness. We hypothesized MBCT to be superior to CBT-RP in this group of treatment-refractory anxiety as MBCT will help persons to become more aware of their bodily sensations, thoughts, and feelings and to take an accepting and tolerating stance towards these long-lasting negative experiences.

2. Material and methods

2.1. Design

Ethical approval for the study was granted by the Ethics Committee of the Leiden University Medical Center (LUMC) (protocol number: P12.039). We designed the study as an open-label Pragmatic randomized Controlled Trial (PrCT) with an experimental condition (MBCT) versus standard psychological relapse prevention treatment for treatment-refractory anxiety disorder (CBT-RP) and repeated measurements at pre-treatment (T1), mid-treatment (T2), post-treatment (T3), and six months follow-up (T4). At each assessment, outcome and mediating variables were assessed by web-based self-report questionnaires administered by Qualtrics. After the conclusion of the experimental part of the study at T3, participants entered a naturalistic follow-up period from T3 to T4 in which they were allowed to seek help the way they would typically do when confronted with an increase of anxiety symptoms.

Participants were recruited between September 2013 and March 2018. The study was performed at PsyQ (Parnassia Bavo group), a large urban ambulatory mental health organization in the Hague, the Netherlands. This center was the first center in the Netherlands to receive a national qualification mark for a top mental health setting specialized in treating more complex and chronic anxiety disorders with evidence-based interventions (such as exposure, response prevention and cognitive therapy in individual and group formats and pharmacotherapy). Based on the available evidence at the designing stage of our study on the effect size for anxiety reduction in controlled studies of mindfulness-based therapy compared to active treatment ([Hofmann et al., 2010](#)), we assumed at least a medium effect (0.50) of MBCT compared to CBT-RP. Therefore, sixty-four participants per study group were needed to detect a minimal clinically relevant difference in BAI scores with a power of 80% and an alpha set at 0.05. After completing the assessment of eligibility, the research assistant randomly assigned participants to conditions using a simple randomization procedure with an online randomizer (<http://www.random.org/lists>). Study participants were fully informed about the nature and purpose of the study. Whereas participants and therapists were aware of the allocated treatment condition, repeated assessments by web-based self-report measures administered through Qualtrics guaranteed blind outcome assessment.

2.2. Participants

Inclusion criteria at baseline assessment were: (a) at least one evidence-based first-line psychological treatment for a primary anxiety disorder (defined as ≥ 20 sessions of individual or group CBT) has been delivered; (b) current Axis-I anxiety disorder according to DSM-IV criteria or still suffering from persistent anxiety symptoms to such an

extent that further treatment was deemed appropriate according to therapist and patient; (c) 18 years or older; (d) willingness to refrain from treatment or counseling more frequently than once a month outside the context of the experimental trial; (e) refraining from alternative meditation training outside the context of the present trial; and (f) willingness to complete homework assignments between sessions. We also included participants with comorbid Axis-I or Axis-II disorders to optimize the study's external validity. The use of antidepressant medication or benzodiazepines was permitted under the condition that the medication dose had been stable for at least three months before inclusion, and participants were willing to keep the dosage on a constant level during the active phase of the trial. Adherence to this rule was regularly checked by the research-assistant. Exclusion criteria were: (a) primary Axis-I diagnosis of substance abuse or dependence; (b) suicidality; and (c) presence of psychotic symptoms.

2.3. Procedure

Participants were informed about the study via therapists, flyers, and posters at the treatment location. If they were interested in participation, they were signed up by their therapist. After that, they were contacted by a research assistant who informed the patient about the study and assessed if they met the in- and exclusion criteria. Participants who met all criteria were asked to give their verbal consent with two weeks to reconsider their participation. Due to scheduling constraints, the time between the baseline assessment and the start of MBCT or CBT-RP varied between two and eight weeks, and consequently the pre-treatment assessment frequently had to be scheduled some weeks later. Two weeks before the pre-treatment assessment participants were informed by the research assistant about their treatment allocation by telephone and were asked to give their final web-based written consent and to complete the pre-treatment assessment. Mid- and post-treatment, as well as follow-up assessments were performed similarly. When participants failed to complete the web-based assessments, they received a reminder after 3 and 5 days.

2.4. Interventions

2.4.1. Mindfulness-based cognitive therapy (MBCT)

The protocol was based on Segal, Williams, and Teasdale (2002), and MBCT was provided in 8 weekly 2-hour group sessions consisting of 4–8 participants. During these sessions, different skills were taught to help participants become more aware and relate differently to their anxious thoughts, feelings, and sensations. Participants were provided a workbook and audiotapes and expected to engage in "homework" between sessions, which could consist of up to an hour of mindfulness practice and exercises each day. The MBCT course covered the following topics. In sessions 1 and 2, participants were taught to become more aware of the habitual 'automatic pilot' way in which information is processed and the distractibility of the mind by automatic thoughts and feelings. Session 3 was devoted to how focusing on breathing can be helpful to stay in the here-and-now. Sessions 4 and 5 focused on the counterproductive effect of avoiding and escaping negative thoughts and feelings compared to an accepting and tolerating stance. In session 6, participants were taught to disengage from negative thoughts by labeling them as thoughts instead of facts. Sessions 7 and 8 focused on relapse prevention.

2.4.2. Cognitive behavioral therapy - relapse prevention (CBT-RP)

The protocol of CBT-RP was based on cognitive-behavioral approaches to prevent worsening of anxiety problems and relapses. The main elements of this treatment were psychoeducation about symptom deterioration and relapse, developing a personal relapse prevention plan and identifying strategies to prevent relapses. Participants received information to better recognize risk factors of symptom worsening. Every participant worked on a personal relapse prevention plan including assessment of individual psychological risk factors for past episodes to

make a personal plan for preventing and cope better with future episodes of enhanced anxiety. As in the MBCT, weekly two-hour sessions were provided in a group consisting of 4–8 participants with a duration of 8 weeks. The participants had to do homework for approximately one hour a week, as compared to up to an hour of daily mindfulness practice and exercises in the MBCT condition.

2.4.3. Therapist training, treatment adherence and competence

In each condition 18 groups were alternately provided by two of the three therapists, with one senior therapist leading all group sessions. All sessions were audiotaped, and regular intervision (two-weekly) took place.

The MBCT therapists were formally trained in the MBCT study protocol, with the senior therapist having three years of experience in delivering MBCT training. Therapist competence and adherence were assessed with the Mindfulness-Based Interventions-Teaching Assessment Criteria (Crane et al., 2012) based on two audio-recorded sessions per trainer. Two independent mindfulness trainers rated the trainers. Mutually agreed on ratings of each of the three trainers were "advanced beginner". CBT-RP follow-up care was given by cognitive-behavioral therapists, with the senior therapist having 15 years of experience in delivering evidence-based CBT for anxiety disorders.

2.5. Measures

2.5.1. Diagnostic assessment

The *Mini-International Neuropsychiatric Interview* (MINI; Sheehan et al., 1998; van Vliet & de Beurs, 2007) was used to establish DSM-IV diagnoses.

2.5.2. Outcome variables

The *Beck Anxiety Inventory* (BAI; Beck, Epstein, Brown, & Steer, 1988) for anxiety severity was the primary outcome measure in the present study (range of Cronbach's α across measurements in the present study: .94 – .96). Secondary outcome measures included: the *Fear Questionnaire* (FQ; Marks & Mathews, 1979; Van Zuuren, 1988) to measure phobic avoidance (range of Cronbach's α of the total scale in the present study: .90 – .92); the *Inventory of Depressive Symptomatology* (IDS; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996) to measure depression severity (range of Cronbach's α in the present study: .88 – .93) and the *World Health Organization Quality of Life Questionnaire-BREF* (WHOQoL-BREF; de Vries & van Heck, 1996; WHOQoL Group, 1998) to measure quality of life into the following four domains: 1. Physical Health; 2. Psychological Health; 3. Social Relationships; 4. Environmental Health. The range of Cronbach's α in the present study was: .80 – .87 for Physical Health; .73 – .83 for Psychological; .62 – .69 for Social Relationships; and .81 – .87 for Environment.

2.5.3. Putative mediating variables

We used the *Five Facet Mindfulness Questionnaire* (FFMQ; Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006; Bohlmeijer, ten Klooster, Fledderus, Veehof, & Baer, 2011; Westerhof & Bohlmeijer, 2011) to measure mindfulness skills along five core dimensions: 1) Observing, 2) Describing, 3) Acting with awareness, 4) Non-judging, and 5) Non-reacting. The range of Cronbach's α of the total scale across measurements in the present study was: .87 – .91. Problems in using emotion regulation strategies were measured with the *Difficulties in Emotion Regulation Scale* (DERS; Gratz & Roemer, 2004) along the following six dimensions: 1) Non-acceptance of emotional responses; 2) Difficulties engaging in goal-directed behavior; 3) Impulse control difficulties; 4) Lack of emotional awareness; 5) Limited access to emotion regulation strategies; and 6) Lack of emotional clarity. The range of Cronbach's α of the total scale in the present study was: .91 – .95. Negative repetitive thinking in the form of worry was measured with the *Penn State Worry Questionnaire* (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990; van Rijsoort, Emmelkamp, & Vervaeke, 1999) (range of

Cronbach's α in the present study: .86–0.91) and in the form of rumination with the *Rumination on Sadness Scales* (RSS; Conway, Csank, Holm, & Blake, 2000; Raes, Hermans, & Eelen, 2003; Roelofs, Muris, Huibers, Peeters, & Arntz, 2006) (range of Cronbach's α in the present study: .89–0.92).

2.5.4. Treatment-related variables

Treatment credibility at pre-treatment was measured with the *Credibility and Expectancy Questionnaire* (CEQ; Borkovec & Nau, 1972).

2.6. Statistical analyses

Preliminary analyses included comparisons between the MBCT and CBT-RP intervention conditions on baseline sociodemographic, outcome, and putative mediating variables, using independent-samples *t*-tests or chi-square tests depending on the nature of the data. Given the longitudinal design of the study, intervention effects were tested on the basis of the intent to treat principle using latent growth curve models (LGCM; Duncan & Duncan, 1995). An advantage of LGCM is that both linear and non-linear change can be analysed, and individuals are allowed to differ on the rate of change in the dependent variables over time. (Duncan & Duncan, 1995, 2009; Muthén & Muthén, 2017).

Using LGCM, we modeled the intercept (i.e., initial status) and slope (i.e., change over time) as latent variables from data at pre-treatment (T1), mid-treatment (T2), post-treatment (T3), and follow-up (T4) assessments. First, unconditional models testing a linear and a non-linear (i.e., quadratic) trend of change in outcome over time were estimated separately in each group. Effect sizes for the rate of change observed in the dependent variables in each group were calculated using Cohen's within-subjects *d*, with 0.2 indicating a small effect, 0.5 a medium effect, and 0.8 a large effect (Cohen, 1988).

Next, the association between condition and change over time was examined by including condition (MBCT vs. CBT-RP coded as 1 and 2, respectively) as a predictor of the growth factors (i.e., intercept and slope). The path from condition to slope reflects group differences on the trajectory of change in the dependent variables over time (see Fig. 1 for a graphical representation of LGCM).

Additionally, we performed a per-protocol (PP) analysis, including only those participants that completed at least four sessions of MBCT or CBT-RP (Kuyken et al., 2008). Specifically, we performed analyses of covariance (ANCOVA) to examine differential effects of treatment condition on mid-, and post-treatment, and follow-up dependent variables.

Next, we performed mediation analyses on an intent to treat basis by testing cross-lagged structural equation models (i.e., CLSEM; Cole & Maxwell, 2003). More specifically, in order to assess possible mediation of the effect of MBCT vs. CBT-RP on anxiety (BAI), by the putative mediating variables (i.e., emotion regulation strategies (DERS),

mindfulness skills (FFMQ), worry (PSWQ), and rumination (RSS)), we performed four separate three-wave CLSEM. We included concurrent (within-time) correlations between the variables, the stability effects for variables (autoregression effects), and longitudinal cross-lagged effects of mediating variables on anxiety over pre-treatment at Time 1 [T1], mid-treatment at Time 2 [T2], and post-treatment at Time 3 [T3]) (see Fig. 2 for a graphical representation of CLSEM).

In these models, we tested whether the intervention condition (i.e. MBCT versus CBT-RP as control condition) had a significant differential effect on anxiety at T3 (Path a, Fig. 1), as well as on mediating variables at T2 (Path b, Fig. 1), and whether mediating variables at T2 predicted anxiety at T3 (Path c, Fig. 1). In order to give a comprehensive picture, we report all separate paths as part of the mediation model. Note that the significance of all these paths is not a requisite for a significant mediation effect (Zhao, Lynch, & Chen, 2010). As a formal mediation test, we estimated the indirect effect of MBCT versus CBT-RP on anxiety at T3 via mediating variables at T2 (Path bc, Fig. 1) using a bootstrapping procedure (Selig & Preacher, 2009). We used 5000 bootstrap to estimate 95% confidence intervals (CI) of the indirect effects (Preacher & Hayes, 2008).

CLSEM has been criticized because within-person processes are not separated from stable between-person differences and consequently lagged parameters may represent stable between-person differences (Hamaker, Kuiper, & Grasman, 2015). In order to check actual within-person relationships between mediating variables and outcome variables, we repeated our analyses separating the within-person processes from stable between-person differences through the inclusion of random intercepts (Hamaker et al., 2015; Mulder & Hamaker, 2021).

We performed LGCM and (RI-)CLSEM based on the intention-to-treat (ITT) principle, including all randomized participants with T1 assessments. Missing data were handled using full information maximum likelihood (FIML) estimations. So, all our models were based on all available data from all randomized participants (intention-to-treat), as this yields unbiased parameter estimates and standard errors, under the assumption of missing at random (Enders, 2010). This assumption was tested using Little's missing completely at random test (Little & Rubin, 1987). Model fit was assessed using the Root Mean Square Error of Approximation (RMSEA; model fit good when <0.05 and satisfactory when <0.08), the Comparative Fit Index (CFI), and the Tucker-Lewis Index (CFI and TLI; model fit good when <0.95 and satisfactory when <0.90); and the Standardized Root Mean Squared Residual (SRMR; model fit good when <0.05 and satisfactory when <0.08) (Hu & Bentler, 1999).

We performed preliminary analyses and ANCOVA with the IBM SPSS Statistics v25.0. (IBM, 2017) and LGCM and (RI-)CLSEM using Mplus v 8 (Muthén & Muthén, 2017).

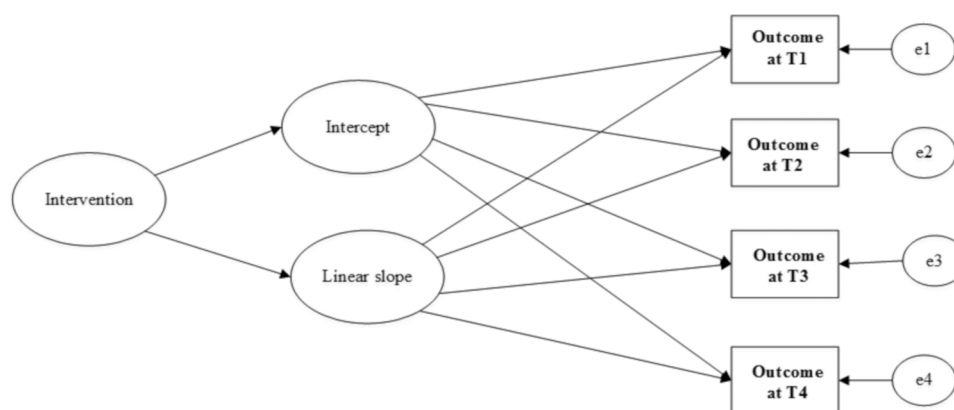


Fig. 1. Latent Growth Curve Model (LGCM) for one outcome measure measured on the four timepoints with intervention condition as predictor. Note. Intervention is Mindfulness-Based Cognitive Therapy (MBCT) versus Cognitive Behavioral Therapy – Relapse Prevention (CBT-RP).

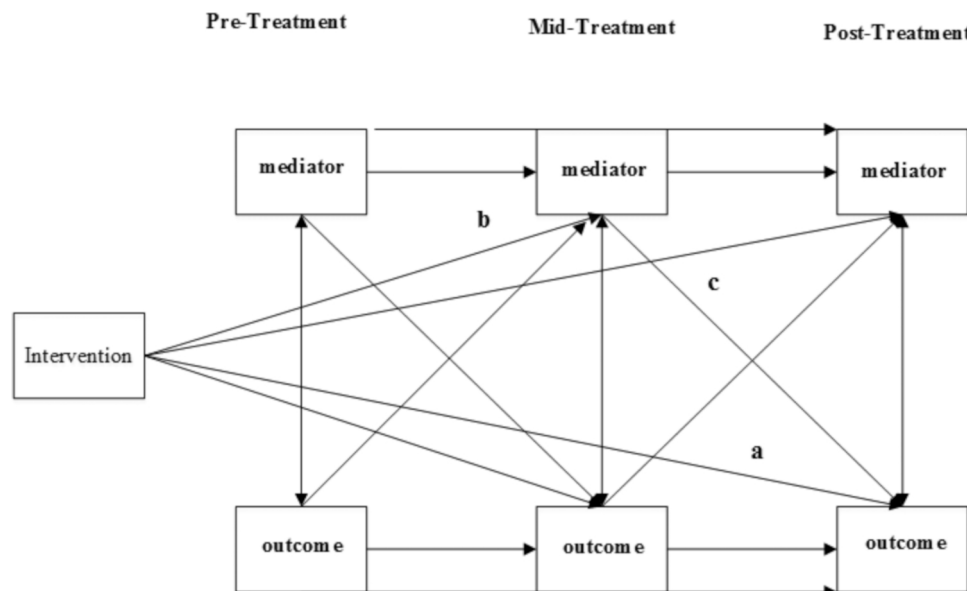


Fig. 2. Cross-lagged panel model of mediation of outcome at post-treatment by mediator at midtreatment. Note. Intervention is Mindfulness-Based Cognitive Therapy (MBCT) versus Cognitive Behavioral Therapy – Relapse Prevention (CBT-RP).

3. Results

3.1. Preliminary analyses

Of the 171 eligible and randomized participants, 136 completed the pre-treatment assessment and were included in the analyses. Of the 36 eligible participants who did not complete the pretreatment assessment, 21 were allocated to MBCT and 15 to CBT-RP ($\chi^2(1) = 1.85, p = .17$).

The 136 participants who completed the pre-treatment assessment had a mean age of 40.8 years ($SD = 13.2$ years; range = 18–73) at the entry of the study, and seventy-nine (58.1%) were female. The most prevalent current anxiety disorders were panic disorder with (25.0%) or without agoraphobia (27.9%), obsessive-compulsive disorder (17.6%), and generalized anxiety disorder (16.9%). Most participants had a single anxiety disorder (49.3%), 25.0% had 2 or more anxiety disorders, and 25.7% were remitted after CBT treatment but were still suffering

Table 1

Descriptive statistics for participants at pre-treatment.

Variable	Total group		MBCT		CBT-RP		MBCT vs CBT-RP	
	M / n	SD / %	M / n	SD / %	M / n	SD / %	t-value / χ^2	p-value
Female, n (%)	79	58.1	35	56.5	44	59.5	0.12	.72
Age at enrolment, M (SD)	40.76	13.02	39.55	12.61	41.77	13.36	0.99	.32
Level of education, n (%)							6.53	.09
Low	13	9.6	2	3.2	11	14.9		
Medium	53	39.0	27	43.5	26	35.1		
High	63	46.3	31	50.0	32	43.2		
Otherwise	7	5.1	2	3.2	5	6.8		
Ethnicity (Caucasian), n (%)	115	84.6	55	88.7	60	81.1	1.50	.22
Living with spouse / partner, n (%)	65	47.8	31	50.0	34	45.9	0.22	.64
Religion, n (%)							3.63	.16
Non-religious	74	54.4	38	61.3	36	48.6		
Christian (Catholic / Protestant)	25	18.4	12	19.4	13	17.6		
Other religion	37	27.2	12	19.4	25	33.8		
MINI diagnosis of anxiety disorder, n (%)								
Panic disorder without Agoraphobia	38	27.9	18	29.0	20	27.0	0.07	.79
Panic disorder with Agoraphobia	34	25.0	11	17.7	23	31.1	3.20	.07
Agoraphobia (without panic disorder)	12	8.8	5	8.1	7	9.5	0.08	.77
Obsessive-compulsive disorder	24	17.6	10	16.1	14	18.9	0.18	.6
Generalized anxiety disorder	23	16.9	10	16.1	13	17.6	0.0	
Social anxiety disorder	17	12.5	10	16.1	7	9.5	1.37	.24
Post-traumatic stress disorder	4	2.9	2	3.2	2	2.7		1.00 ^a
Specific phobia	3	2.2	3	4.8	0	0.0		.09 ^a
MINI number of anxiety disorder, n (%)							3.53	.47
0	35	25.7	19	30.6	16	21.6		
1	67	49.3	28	45.2	39	52.7		
> 2	34	25.0	15	24.2	19	25.7		
MINI diagnosis of depressive disorder, n (%)	22	16.2						
Duration of anxiety complaints in years, M (SD)	7.68	3.39	7.89	3.41	7.51	3.39	0.55	.38
Treatment credibility ^b	5.98	1.72	6.02	5.94	1.85	7.39	0.30	.77

Note. MBCT = Mindfulness-based Cognitive Therapy; CBT-RP = Relapse Prevention-Cognitive Behavioral Therapy; Level of education: low = primary school; medium = lower and upper secondary education; high = higher vocational and academic education; MINI = Mini-International Neuropsychiatric Interview; ^a Fisher's Exact Test; ^b mean item score on four 0–10 point VAS rating scales

persistent residual anxiety symptoms. Of these remitted participants the anxiety diagnoses at admission were: obsessive-compulsive disorder (OCD): 37.1%; PD: 33.7%; GAD: 25.7%; SAD: 22.9%; Agoraphobia without PD: 5.7%; and Specific phobia: 5.7%. The mean duration of self-reported anxiety complaints was 7.7 years ($SD = 3.4$). As can be derived from Table 1 participants in the MBCT ($n = 62$) and CBT-RP condition ($n = 74$) did not significantly differ on any of the sociodemographic or clinical variables according to independent-samples t -tests or chi-square tests (range of p -values: .07 – 1.00). Also, their ratings of treatment credibility and outcome expectancies were comparable ($p = .77$), with a mean total score of around six on a scale from 0 to 10, indicating that treatment credibility was just sufficient. Pre-treatment outcome and mediating variables (see Table 2) also proved to be comparable according to independent-samples t -test (range of p -values: .07 – .93). Fig. 3 illustrates the flow of participants and shows that data loss (lost to follow-up) was 22.8% at post-treatment, and 31.6% at follow-up. Little's test showed that data were missing completely at random ($\chi^2(171) = 165.55$; $p = .60$).

3.2. Outcome analyses using LGCM

First, linear and non-linear (i.e., quadratic) trends of the dependent variables from pre-treatment to follow-up time were tested using unconditional models of change. Also, after including non-linear trends, the fit of almost all of the 22 models remained poor mainly due to a non-positive latent variable covariance matrix related to the follow-up measurements. Therefore, these unconditional models of change were repeated, excluding follow-up measurements. The linear trend of the unconditional models presented good fit indices to the observed data (see Appendix A) and was not further improved by including non-linear trends. As can be derived from Table 2, in the MBCT condition, the within-subjects effect sizes for the rate of change from T1 to T3 in anxiety (BAI), depression (IDS), and rumination (RSS) were medium

(>0.5), while the effect sizes for the rate of change in mindfulness skills (FFMQ), difficulties in emotion regulation strategies (DESR), and worry (PSWQ) were large (>0.8). Effects on avoidance (FQ) and quality of life (WHOQoL) were small (>0.2) or negligible (<0.2). In the CBT-RP condition, all effect sizes for the rate of change from T1 to T3 in outcome and mediating variables were small or negligible. Table 2 also shows that pretreatment-follow-up effect sizes are somewhat smaller than pretreatment-posttreatment effect sizes. However, within-subjects Cohen's d for anxiety, mindfulness skills, difficulties in emotion regulation strategies, worry, and rumination in the MBCT condition still had a medium value (>0.50).

Next, we performed conditional models with intervention condition (MBCT versus CBT-RP) as a predictor of the growth factors. The conditional models provided satisfactory to excellent fit indices to the observed data (see Appendix B). In none of the 11 models did intervention condition predict variation in the intercept, indicating that the groups did not differ in outcome and mediation variables at pretreatment (range of p -values: .06 – 0.94). On the other hand, condition was a significant predictor of change over time observed in 6 of the 11 dependent variables (see Table 4). Specifically, the MBCT group showed a significantly greater decrease than the CBT-RP group in anxiety (BAI: $p = .03$), avoidance (FQ: $p = .01$), difficulties in emotion regulation strategies (DESR: $p < .001$), and worry (PSWQ: $p < .001$), as well as a significantly greater increase in mindfulness skills (FFMQ: $p < .001$) and quality of social relationships (WHOQoL: $p = .02$). The effect of condition on rumination (RSS) was borderline significant ($p = .07$).

3.3. Mediation analyses using CLSEM

Each of the four CLSEM yielded satisfactory to excellent fit statistics (see Table 3). See Appendices C to F for a complete overview of all pathways of the separate models. The autoregressive correlations of the models showed that both anxiety severity (range: .59 – 0.70) as well as

Table 2

Means and standard deviations of outcome and mediator variables.

	Pre-treatment (T1)		Midtreatment (T2)		Posttreatment (T3)		d between		Follow-up (T4)		d between	
	M	SD	M	SD	M	SD			M	SD		
MBCT												
BAI	19.56	11.53	16.50	10.01	13.70	10.64	.39	.74	14.16	11.09	.29	.56
FQ	41.52	21.35	40.01	20.01	37.67	20.55	.19	.36	39.22	21.68	.04	.23
IDS	26.85	13.45	23.73	15.23	21.28	13.98	.23	.60	22.69	16.57	.14	.36
WHO:1	55.09	18.18	57.19	18.63	58.16	20.63	.08	.22	57.07	21.23	.19	.13
WHO:2	54.92	13.34	56.61	15.69	58.63	16.83	.16	.31	57.37	15.66	.17	.27
WHO:3	57.19	19.24	57.31	19.32	60.65	17.23	.17	.31	57.91	19.02	.12	.05
WHO:4	67.88	15.06	66.47	15.29	67.09	17.58	.03	.06	67.74	16.17	.13	.02
FFMQ	112.93	15.82	120.03	15.32	128.11	18.36	.32	.86	123.92	16.28	.12	.77
DESR	101.82	21.00	89.71	22.52	82.26	22.78	.46	1.09	85.50	24.51	.14	.99
PSWQ ^a	37.48	6.28	35.49	6.06	32.60	5.71	.52	.89	34.19	6.63	.25	.60
RSS	37.10	8.88	33.90	8.75	31.18	9.39	.27	.67	32.65	9.71	.01	.53
CBT-RP												
BAI	21.31	13.78	18.73	12.11	18.52	13.81		.29	17.71	13.33		.33
FQ	41.88	22.31	41.08	23.49	41.48	20.47		.04	40.13	23.09		.14
IDS	28.03	14.79	26.06	15.93	24.51	14.44		.36	25.01	16.44		.26
WHO:1	52.43	15.91	53.94	18.67	56.60	17.53		.36	52.98	20.80		.03
WHO:2	53.53	13.76	56.10	14.58	56.08	13.68		.25	54.46	17.49		.16
WHO:3	58.91	21.26	60.78	18.77	57.65	18.50		.12	60.31	22.29		.07
WHO:4	66.62	13.10	67.87	14.27	66.65	15.03		.00	65.63	15.17		.10
FFMQ	118.16	17.27	121.02	19.06	122.06	19.42		.35	121.95	17.69		.28
DESR	98.86	23.42	96.99	25.33	93.18	24.82		.33	89.05	25.82		.51
PSWQ	36.62	5.48	35.75	5.81	35.62	5.78		.24	35.86	6.70		.16
RSS	36.25	9.85	34.38	10.02	33.91	10.43		.27	32.79	9.64		.47

Note. MBCT = Mindfulness-based Cognitive Therapy; CBT-RP = Relapse Prevention-Cognitive Behavioral Therapy; BAI = Beck Anxiety Inventory; FQ = Fear Questionnaire; IDS = Inventory of Depressive Symptoms; WHO = WHOQoL-Bref; WHO:1 = Physical Health; WHO:2 = Psychological Health; WHO:3 = Social Relationships; WHO:4 = Environmental Health; FFMQ = Five Facet Mindfulness Questionnaire; DESR = Difficulties in Emotion Regulation Questionnaire; PSWQ = Penn State Worry Questionnaire; RSS = Rumination on Sadness Scale; LGCM estimates at T1, T2 and T3 using T1 - T3 measurements; LGCM estimates at T4 using T1 - T4 measurements; ^a In the present study, we used a 3-point Likert-scale for the PSWQ (not at all, somewhat, very typical of me); Cohen's d between-subjects was calculated as the difference between the means divided by the pooled SD; Cohen's d within-subjects between T1-T3 and T1-T4 was calculated by dividing the mean difference by the standard deviation of the difference.

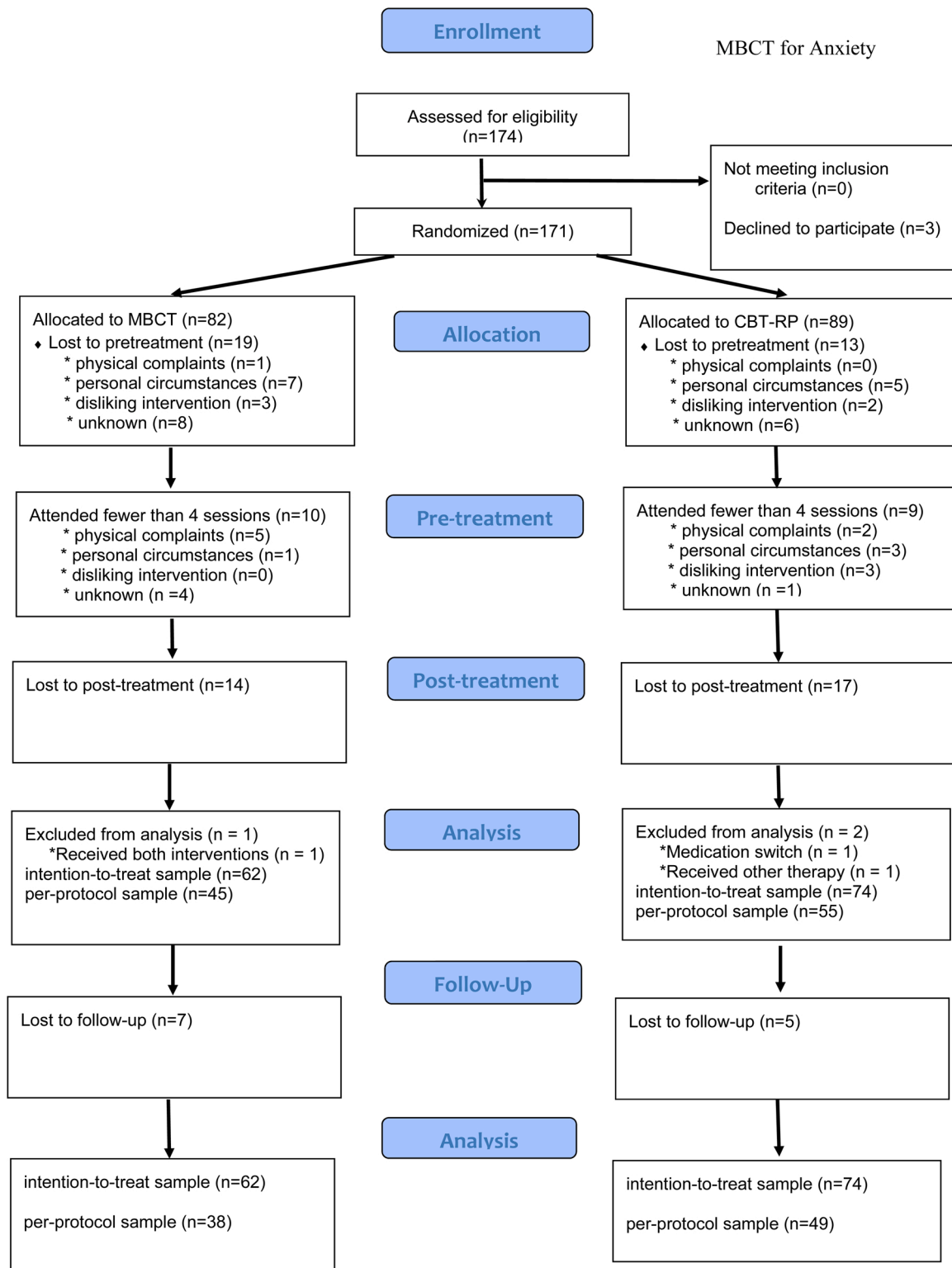


Fig. 3. Flow of participants.

mediating variables (range.50 –0.73) were predicted by the same variable at an earlier time point, indicating that these variables were relatively stable over time (T1, T2, T3). Concurrent correlations showed that within-time mediating variables and outcome variables were less strongly correlated (range.13 –0.53), indicating a consistent but less strong relationship than autocorrelations.

Overall, CLSEM results confirmed the intervention effects as found

with LGCM showing that MBCT successfully decreased anxiety (range beta values:.09 –0.11). In comparison to CBT-RP, MBCT was also more effective in enhancing mindfulness skills and reducing difficulties in emotion regulation strategies and worry at T3 (range beta values:.11 –0.20), but not rumination on sadness (beta value:.10) (see [Appendices C-F](#)).

None of the mediating variables at T2 significantly predicted anxiety

Table 3

Model fit statistics for cross-lagged structural equation models with BAI T3 as outcome.

Model	χ^2 (df)	RMSEA (90CI)	CFI	TLI	SRMR
FFMQ T2 as mediator	6.93 (4)	.07 (0.00–0.16)	.99	.97	.05
DERS T2 as mediator	7.95 (4)	.08 (0.00–0.17)	.99	.96	.03
PSWQ T2 as mediator	1.95 (4)	.00 (0.00–0.09)	1.00	1.00	.02
RSS T2 as mediator	5.80 (4)	.06 (0.00–0.15)	.99	.98	.03

Note. RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; SRMR = Standardized Root Mean Square Residual; BAI = Beck Anxiety Inventory; FQ = Fear Questionnaire; FFMQ = Five Facet Mindfulness Questionnaire; DERS = Difficulties in Emotion Regulation Questionnaire; PSWQ = Penn State Worry Questionnaire; RSS = Rumination on Sadness Scale

at T3 (except for DERS T2 scores predicting BAI T3 scores). Moreover, there was no indirect effect from the intervention condition on anxiety at T3 via mediating variables at T2 (path bc) (range of p-values: .34–.97). Only the bc path from intervention condition via DERS at T2 to BAI at T3 approached significance (beta = 0.03; SD = 0.01; p = .06; 95% CI [0.00–0.05]) (see Table 5 and Appendices C–F).

3.4. Post hoc sensitivity analyses

We repeated our analyses separating the within-person processes from stable between-person differences through the inclusion of random intercepts in order to check actual within-person relationships between mediating variables and outcome variables (Hamaker et al., 2015). Overall, these between-person models showed similar results to the “traditional” cross-lagged panel models described above (see Appendix G and H).

Moreover, by using a dichotomous variable for intervention condition (MBCT versus CBT-RP) as an independent variable in our models, the other estimated pathways were forced to be the same for all participants irrespective of the intervention condition. In order to check whether it was justified to model these pathways for the entire sample, we reran the CLSEM while testing whether the crossed pathways (from mediating variables at T2 to outcome variables at T3) significantly differed across conditions. The results indicated no significant differences between intervention conditions on any of the crossed paths (difference scores between –0.08 and 0.15; ps > 0.19).

Table 4

Conditional latent curve growth model with rate of change (slope) in total sample and intervention condition as predictor of rate of change on outcome and mediating variables.

Variables	Slope		Slope on intervention	
	B	p	B	p
BAI	-4.69	< 0.001	1.76	.03
FQ	-4.26	.005	2.08	.01
IDS	-0.77	.02	0.10	.26
WHO:1	0.22	.59	0.05	.70
WHO:2	0.53	.23	-0.04	.72
WHO:3	0.97	.01	-0.28	.02
WHO:4	-0.48	.39	0.14	.42
FFMQ	2.12	< 0.001	-0.44	< 0.001
DERS	-1.77	< 0.001	0.36	< 0.001
PSWQ	-1.98	< 0.001	0.43	< 0.001
RSS	-1.50	.01	0.27	.07

Note. BAI = Beck Anxiety Inventory; FQ = Fear Questionnaire; IDS = Inventory of Depressive Symptoms; WHO = WHOQoL-Bref; WHO:1 = Physical Health; WHO:2 = Psychological Health; WHO:3 = Social Relationships; WHO:4 = Environmental Health; FFMQ = Five Facet Mindfulness Questionnaire; DERS = Difficulties in Emotion Regulation Questionnaire; PSWQ = Penn State Worry Questionnaire; RSS = Rumination on Sadness Scale

3.5. Per protocol analysis

Fifty-two of the 62 MBCT (83.9%) and 65 of the 74 CBT-RP participants (87.8%) completed at least 4 of the eight sessions ($\chi^2(1) = 0.44$, $p = .34$). Completers attended on average 7.02 (SD = 1.38) out of the eight MBCT sessions and 6.98 (SD = 0.88) out of the eight CBT-RP sessions. No significant differences were found regards sociodemographic characteristics or pre-treatment scores on outcome and mediating variables between adherent and non-adherent participants according to independent-samples *t*-tests or chi-square tests (range of p-values: .10–0.98).

Little's test showed that data were missing completely at random ($\chi^2(160) = 158.24$; $p = .52$). The PP analysis using available assessments in treatment completers with ANCOVA confirmed the differential effects of treatment at post-treatment for anxiety (BAI), avoidance (FQ), mindfulness skills (FFMQ), difficulties in emotion regulation strategies (DERS), and worry (PSWQ) as found in the conditional LGCM. The differential effect on rumination (RSS) that was borderline significant in the intention-to-treat conditional LGCM also became significant. In contrast, the differential effect on quality of social relationships (WHOQoL) failed to reach significance (see Appendix I). As post-treatment data in 17 (MBCT: $n = 7$; CBT-RP: $n = 10$) of the 116 treatment completers were missing (14.6%), differences in pre-treatment characteristics of adherent participants with complete and missing data were examined using independent-samples *t*-tests or chi-square tests if appropriate and no significant pre-treatment differences were observed (range of p-values: .09–0.90). At follow-up, only the differential effects for mindfulness skills ($p = .02$), difficulties in emotion regulation strategies ($p = .05$), and worry ($p = .02$) remained (borderline significant (in line with the smaller effect sizes for the rate of change on outcome and mediating variables at follow-up compared to post-treatment)).

4. Discussion

4.1. Treatment outcome

The primary aim of the present open-label Pragmatic randomized Controlled Trial (PrCT) was to examine the effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) for persons that responded insufficiently to evidence-based first-line psychological treatment for their anxiety disorder compared to Relapse Prevention-Cognitive Behavioral Therapy (CBT-RP) in a clinical setting representative of a routine clinical care setting. Anxiety ($M = 20.5$) and avoidance scores ($M = 41.7$) of participants at baseline showed that the symptom severity of our sample was comparable to that of a representative sample of Dutch persons with comorbid anxiety and depression disorder ($M = 20.6$, resp. 38.6) and higher than that of persons with anxiety disorder only ($M = 14.3$, resp. 29.0) (Lamers et al., 2011). When compared with the CBT-RP group, at post-treatment, the MBCT group showed a significantly larger decrease in self-reported anxiety and avoidance, while changes in depression severity and quality of life were comparable.

The medium large within-subjects effect sizes for the pre- to post-treatment and the pre- to follow-up changes in anxiety severity are similar to those reported for mindfulness-based treatment addressing anxiety (Khouri et al., 2013). Moreover, our results extend the previous finding on MBCT as an adjuvant to the continuation of pharmacotherapy (Giommi et al., 2021; Kim et al., 2009; Ninomiya et al., 2020) in the treatment of treatment-refractory anxiety patients by showing that MBCT is also effective as a stand-alone intervention compared to CBT-RP provided in a similar group treatment format as MBCT. Moreover, this is the first study to show that MBCT may also be effective in patients who responded insufficiently to evidence-based CBT as a first-line treatment provided for at least 20 sessions.

In contrast to the more pronounced long-term effects of MBCT on anxiety severity in the study of Giommi et al. (2021), in the present

Table 5

Results for the mediation pathways with BAI at T3 as outcome variables.

Mediator	Predictor	Outcome	Path	B	95% CI	p
FFMQ	Intervention	BAI T3	a	0.11 (0.05)		.02
	Intervention	FFMQ T2	b	-0.08 (0.06)		.17
	FFMQ T2	BAI T3	c	-0.09 (0.05)		.09
	Intervention via FFMQ T2	BAI T3	bc	0.02 (0.02)	[- 0.01, 0.02]	.34
DERS	Intervention	BAI T3	a	0.09 (0.05)		.06
	Intervention	DERS T2	b	0.19 (0.06)		.001
	DERS T2	BAI T3	c	0.14 (0.06)		.03
	Intervention via DERS T2	BAI T3	bc	0.03 (0.01)	[0.00, 0.05]	.06
PSWQ	Intervention	BAI T3	a	0.10 (0.5)		.03
	Intervention	PSWQ T2	b	0.07 (0.06)		.23
	PSWQ T2	BAI T3	c	0.05 (0.05)		.36
	Intervention via PSWQ T2	BAI T3	bc	0.01 (0.01)	[- 0.01, 0.01]	.53
RSS	Intervention	BAI T3	a	0.11 (0.05)		.03
	Intervention	RSS T2	b	0.06 (0.07)		.37
	RSS T2	BAI T3	c	0.10 (0.06)		.07
	Intervention via RSS T2	BAI T3	bc	0.01 (0.01)	[- 0.01, 0.02]	.47

Note. BAI = Beck Anxiety Inventory; FFMQ = Five Facet Mindfulness Questionnaire; DERS = Difficulties in Emotion Regulation Questionnaire; PSWQ = Penn State Worry Questionnaire; RSS = Rumination on Sadness Scale; T1 = pretreatment; T2 = midtreatment; T3 = posttreatment

study the effect of MBCT on anxiety severity at post-treatment diminished from .74 to .56 at follow-up. A recent (network) meta-analysis for prevention and time to depressive relapse (McCartney et al., 2021) showed that booster sessions at regular intervals might result in a higher effectiveness of MBCT, although little is known about timing, frequency, and attendance at booster sessions. Future studies are needed to examine whether short-term treatment effects in (refractory) anxiety also can be maintained or enlarged by providing regular booster sessions.

4.2. Mediation and working mechanisms

A secondary aim of our study was to explore candidate mediating variables to identify possible mechanisms of change allowing further treatment improvement. The present study is one of the first with three time points allowing examination of the precedence of changes in mediators in relation to subsequent changes in outcomes (Kazdin, 2007). When compared with the CBT-RP group, at post-treatment, the MBCT group showed a significantly larger decrease in difficulties in emotion regulation and worry, as well as a significantly larger increase in mindfulness skills. These results are in line with those of previous studies showing that MBCT is effective in increasing mindfulness skills and reducing difficulties in emotion regulation strategies and worry with medium to large within-subjects effect sizes and small to medium between-subjects effect sizes compared to active control conditions (Alsubaie et al., 2017; Gu et al., 2015; Maddock & Blaire, 2021; Monterege, Tsagkalidou, Cuijpers, & Spinhoven, 2020; van der Velden et al., 2015).

However, our mediation hypothesis was not confirmed as formal mediation analyses showed that none of the indirect paths from treatment to anxiety at post-treatment via the putative mediators at mid-treatment was statistically significant. So, although anxiety severity and mediators proved to have moderately strong cross-sectional associations, temporal precedence of changes in mediators regards subsequent changes in anxiety could not be established, making causal inferences about mediators unlikely.

In the literature, a distinction is made between universal candidate mediators or mechanisms of change, universal mechanisms that may have specific manifestations in special populations and mechanisms specific to particular populations (e.g., decentering from negative thinking with depression) (Alsubaie et al., 2017; Teasdale, Segal & Williams, 2003). As we examined a broad array of candidate mediators, including presumed universal mediators (such as mindfulness skills) and also worry (i.e., a specific manifestation of the universal mechanism of repetitive negative thinking involved in the onset and maintenance of

anxiety (Spinhoven, van Hemert, & Penninx, 2018; Watkins, 2008), it seems unlikely that the absence of mediation effects is due to our choice of candidate mediators. Although a third variable explanation can never be excluded, a more likely explanation for our present results is that to identify mediators and working mechanisms, several methodological improvements have to be realized. (a) As most available studies, we relied on self-report measures of mediators and outcomes, and results may be biased by shared method variance. Kazdin (2007) already indicated the need to consider different measurement perspectives, including neuropsychological and experimental measures. Triangulating experimental, neuroscience, and self-report measures to test potential biological, psychological, and social processes might lead to a better understanding of how mindfulness-based interventions work (Alsubaie et al., 2017) and to explore examination of alternative mechanisms (such as brain networks involved in the regulation of self-referential thought processes (Zeidan, Martucci, Kraft, McHaffie, & Coghill, 2014)). (b) Our study was adequately powered to detect medium sized differential treatment effects but no a prior statistical power analysis for the mediation models was performed. Using an intention-to-treat approach our study had enough statistical power to detect medium to large mediation effects in path models using bootstrapping procedures (Sim, Kim, & Suh, 2022), but not to detect mediation effects involving small effects for the a and/or b paths in the mediation models (Fritz and MacKinnon, 2007; Sim et al., 2022); (c) Available studies typically assess mediators and outcomes at two or three time points, and the interval length may or may not be explicitly justified. At the same time, technological advances have led to an increase in the use of intensive longitudinal data (e.g., using experience sampling methods (ter Avest et al., 2020)). Exploring mediation in an (intensive) longitudinal context may enhance our understanding of mechanisms of change on a smaller time scale that would not be possible to make with sparser data (Berli, Inauen, Stadler, Scholz, & Shrout, 2021). It is quite conceivable that critical mediating processes occur in the context of MBCT sessions or formal or informal practice and are not captured by our present gross measurements. Using such intensive longitudinal designs, it is also important to evaluate the most appropriate statistical mediation models as e.g. parallel process models of mediation typically assesses mediation effects for contemporaneous change as opposed to mediation effects for longitudinal change in which prior change in the mediator is related to subsequent levels in the outcome variable (MacKinnon, 2008), and many models do not separate within-person variance from between-person variance while associations on the within-person level are more likely to point to a causal process than associations on the between-person level (Hamaker et al.,

2015).

4.3. Study limitations

Although the current trial has high ecological validity because of its pragmatic design, the following study limitations must be taken into account in interpreting the findings of the present pragmatic randomized controlled trial with due caution: (a) Treatment-refractory anxiety disorder is poorly defined in the literature with most studies requiring only pharmacological treatment failure. Although the present study required psychological treatment failure, future studies should operationalize treatment-refractory anxiety more precise as present after both at least one specified first-line pharmacological and one specified psychological treatment failure provided for an adequate duration with anxiety severity remaining above a specified threshold (Bokma et al., 2019); (b) In this open-label trial, the research assistant performed the simple randomization procedure following eligibility assessment and treatment allocation was not concealed for participants during the pre-treatment and subsequent assessments. Although attrition before pre-treatment proved to be unrelated to condition and there were no significant differences between conditions on the pre-treatment assessments (including treatment expectancy), attrition bias cannot be excluded. (c) Sample size did not allow to analyse facets of mindfulness skills and difficulties in emotion regulation as analysing the five subscales of the FFMQ and six subscales of the DESR without correcting for chance capitalization would have resulted in a high probability of making Type 1 errors. (d) MBCT therapists' competence and adherence was rated as 'advanced beginner'. Possibly 'competent', 'proficient' or 'advanced' MBCT therapists would have obtained even better treatment results. (e) No data on prior experience with mindfulness or meditation (as treatment or otherwise) were available. (f) No data on prior treatment history before admission at our center or the treatment format (individual, group or combined) of the first line CBT at our center were available.

4.4. Conclusions

MBCT seems to be a promising intervention in routine clinical care for persons with an anxiety disorder who insufficiently responded to first-line psychological CBT treatment. Providing regular booster sessions may be needed to maintain or enlarge short-term treatment effects. Future research in larger samples assessing long-term effects and using intensive longitudinal designs to identify possible working mechanisms is called for.

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Data statement

Due to ethical concerns, supporting data cannot be made openly available. Further information about the data and conditions for access are available by contacting the corresponding author.

Data Availability

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.janxdis.2022.102599](https://doi.org/10.1016/j.janxdis.2022.102599).

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