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Research paper

Patients with a preference for medication do equally well in mindfulness-based cognitive therapy for recurrent depression as those preferring mindfulness

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ABSTRACT

Background: Previous studies have suggested that patients' treatment preferences may influence treatment outcome. The current study investigated whether preference for either mindfulness-based cognitive therapy (MBCT) or maintenance antidepressant medication (mADM) to prevent relapse in recurrent depression was associated with patients' characteristics, treatment adherence, or treatment outcome of MBCT.

Methods: The data originated from two parallel randomised controlled trials, the first comparing the combination of MBCT and mADM to MBCT in patients preferring MBCT ($n=249$), the second comparing the combination to mADM alone in patients preferring mADM ($n=68$). Patients' characteristics were compared across the trials ($n=317$). Subsequently, adherence and clinical outcomes were compared for patients who all received the combination ($n=154$).

Results: Patients with a preference for mADM reported more previous depressive episodes and higher levels of mindfulness at baseline. Preference did not affect adherence to either MBCT or mADM. With regard to treatment outcome of MBCT added to mADM, preference was not associated with relapse/recurrence ($\chi^2=0.07$; $p=.80$), severity of (residual) depressive symptoms during the 15-month follow-up period ($\beta=-0.08$, $p=.49$), or quality of life.

Limitations: The group preferring mADM was relatively small. The influence of preferences on outcome may have been limited in the current study because both preference groups received both interventions.

Conclusions: The fact that patients with a preference for medication did equally well as those with a preference for mindfulness supports the applicability of MBCT for recurrent depression. Future studies of MBCT should include measures of preferences to increase knowledge in this area.

1. Introduction

Major depressive disorder (MDD) is a common and highly debilitating mental disorder that is characterized by high rates of relapse or recurrence (Richards, 2011). To date, the most commonly used treatment to prevent future episodes of MDD is the use of maintenance antidepressant medication (mADM). Although there is evidence that mADM are more effective than placebo in reducing the risk of relapse (Borges et al., 2014; Kaymaz et al., 2008), adherence to mADM is generally low (Bockting et al., 2008) and the prophylactic effectiveness seems to decrease with the number of previous episodes (Kaymaz et al., 2008). Therefore, alternative preventive strategies have been developed. For example, Mindfulness-Based Cognitive Therapy (MBCT; Segal et al. (2012)) significantly reduces relapse risk in patients with three or more previous depressive episodes (Piet and Hougaard, 2011) and appears to be at least as effective as mADM in the prevention of relapse (Kuyken et al., 2008; Kuyken et al., 2015; Segal et al., 2010). This suggests that MBCT offers a viable alternative for patients preferring a psychological intervention to prevent relapse.

In general, practice guidelines recommend that patients'

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treatment preferences should play an important role in the selection of a treatment modality (American Psychiatric Association (APA), 2010). In the context of the acute phase of depression treatment, depressed patients have been shown to generally prefer psychological rather than pharmacological treatment (Steidtmann et al., 2012; van Schaik et al., 2004). This suggests that many patients with recurrent depression might prefer psychological treatment, such as MBCT, over mADM to prevent relapse/recurrence.

Treatment preferences seem to be related to treatment expectations and therefore, may contribute to adherence and outcomes as a non-specific therapeutic factor (Rutherford et al., 2010). Although several studies on the acute treatment of depression have examined the impact of preferences on outcome, results are inconclusive. A systematic review on treatment preferences in MDD concluded that preferences may positively affect treatment initiation and the therapeutic alliance, but have minimal impact on depression severity outcomes (Gelhorn et al., 2011). In contrast, a simultaneous meta-analysis indicated a small (Cohen's $d=0.31$) but significant benefit of preference-match in patients with psychiatric problems receiving psychological or pharmacological therapies (Swift et al., 2011). For the subset of studies specifically looking at depression ($k=12$), this effect was also small ($d=0.35$) but significant. The inconsistency in the literature on the effects of preference on treatment outcome may be related to differences in methodology. For example, in an RCT comparing behavioural activation and antidepressant medication, preference for psychotherapy influenced treatment outcome in terms of clinician-rated depression, but not self-rated depression (Moradveisi et al., 2014). In addition, the strength of patient preference on a continuous measure may be more predictive of outcome than preference-match as a categorical predictor (Raue et al., 2009).

Unlike most patient characteristics, preferences cannot be randomly allocated because of their intrinsic relationship with the received treatment. In this way, preferences can affect the external and internal validity of randomised controlled trials (RCTs) (Corrigan and Salzer, 2003). For instance patients with a strong preference for psychological treatment are likely to decline RCTs precluding their preference (van Schaik et al., 2004). Consequently, RCTs may underestimate the effect of preferences on outcome. In addition, preferences may affect the internal validity of a trial, for example because patients who receive a treatment concordant with their preference are less likely to drop out, show higher rates of attendance and have a better working alliance with the therapist (Elkin et al., 1999; Iacoviello et al., 2007; Kwan et al., 2010; Raue et al., 2009). These methodological problems related to preferences may lead to a gap between results obtained in RCTs and routine practice (TenHave et al., 2003).

To our knowledge, no studies have explicitly examined patient preferences and their possible relation with treatment adherence and treatment outcome in relapse/recurrence prevention of MDD. In two parallel randomised controlled trials (the first comparing the combination of MBCT and mADM to MBCT alone, the second comparing the combination to mADM alone), patients could choose to participate in either study, according to their preference for either mADM or MBCT. The current post-hoc study aims to investigate: (a) possible differences in demographic and clinical characteristics between patients with a preference for MBCT and those with a preference for mADM; (b) whether patients' preferences are associated with adherence to MBCT or adherence to mADM; and (c) whether patients' preferences are associated with relapse/recurrence risk, severity of depressive symptoms, or quality of life, over the 15 months follow-up. We had no specific a priori hypotheses with regard to possible differences in patients' baseline characteristics, but we expected MBCT treatment adherence and clinical outcome to be better for patients preferring MBCT than for patients preferring mADM.

2. Methods

2.1. Study design

The study design and procedures are presented in full in the published study protocol (Huijbers et al., 2012) and are summarised below. Originally we intended to conduct a three-armed RCT of MBCT alone, mADM alone or MBCT+mADM, but due to strong treatment preferences this turned out not to be feasible. Therefore we ended up conducting two parallel RCTs (see Fig. 1). Patients preferring MBCT participated in an RCT comparing the combination of MBCT and mADM to MBCT alone, i.e. with discontinuation of mADM (Huijbers et al., In press). Patients preferring to continue their mADM participated in an RCT comparing the combination of MBCT and mADM to mADM alone (Huijbers et al., 2015). This change in design enabled us to acknowledge patients' preferences while maintaining the experimental rigour of randomisation. In addition, it provided the opportunity to study the possible effect of treatment preference in depression relapse/recurrence prevention.

2.2. Participants and procedure

Patients were recruited in 12 secondary and tertiary psychiatric outpatient clinics across the Netherlands between September 2009 and January 2012. Patients were referred by mental health care professionals or recruited by advertisements in the media (TV, magazines and newspapers). Inclusion criteria were a history of at least three previous depressive episodes according to the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV), being in full or partial remission; currently treated with mADM for at least 6 months; 18 years of age or older; and Dutch speaking. The study was approved by the Medical Ethics Committee Arnhem-Nijmegen (nr. 2008/242) for all participating sites. After full explanation of the study, written informed consent was obtained from all participants. The study period was 15 months with assessments at 0 (baseline), 3, 6, 9, 12 and 15 months. For the possible differences between patients who preferred to participate in trial A (preference for MBCT) and trial B (preference for medication) we used data of all participants ($n=317$). For all others analyses we only used data from the participants who received the combination of MBCT and mADM ($n=121+33$).

2.3. Intervention: MBCT plus maintenance ADM (MBCT+mADM)

MBCT was delivered in 12 different centres across the Netherlands according to the, slightly adapted, protocol by Segal, Williams and Teasdale (Segal et al., 2002). It was delivered in groups of 8–12 participants and consisted of eight weekly sessions of 2.5 h plus one day of silent practice between the 6th and 7th session (Kabat-Zinn, 2013). Participants were encouraged to practice meditation at home for about an hour a day with the support of CDs.

For continuation of mADM, a minimum of one consultation with a psychiatrist was recommended. Psychiatrists were instructed to maintain or reinstate a therapeutic dosage of mADM, and recommendations to manage side effects were provided. Adherence to the mADM protocol was defined as using a therapeutic dose at each follow-up contact during the observed time period (using last observation carried forward for participants who did not complete all assessments).

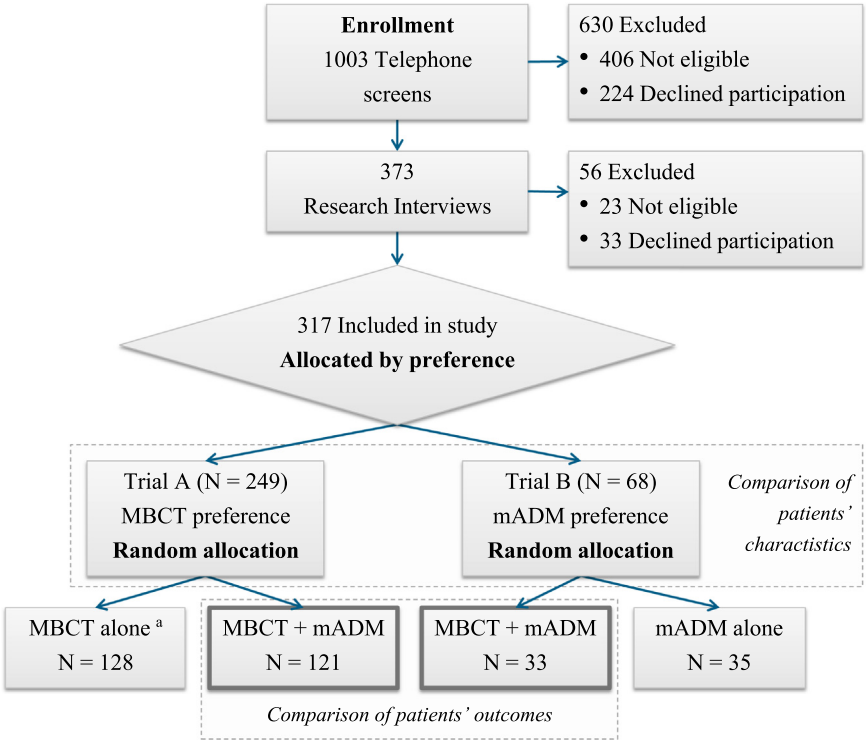

Fig. 1. Schematic overview of the two trials and random allocation to treatments.

2.4. Preference measures

Preference for MBCT was operationalised as choosing to participate in trial A (MBCT+mADM versus MBCT alone) and preference for mADM as choosing to participate in trial B (MBCT+mADM versus mADM alone).

Preference strength was measured at baseline with an adapted version of the Treatment Credibility Questionnaire (TCQ; (Borkovec and Nau, 1972) by Addis et al. (2004), with one additional item from the Credibility Expectancy Questionnaire (Devilly and Borkovec, 2000). The TCQ that was used in this study originally consisted of 7 items that focus on credibility and expectancy: "To what extent do you think this treatment will help you?", "How logical does this treatment appear to you?", "How scientific does this treatment appear to you?", "To what extent do you think that this treatment will help you to better understand the causes of your problems?", "To what extent do you think that you will learn effective strategies to cope with your problems in this treatment?", "To what extent does this treatment correspond to your ideas about what helps people in treatments?" and "To what extent do you feel that this treatment will reduce your complaints?". For the current study, we excluded items 4 and 5 from the analyses because these seemed to be less applicable to mADM, resulting in an adapted 5-item version of the scale. Items were scored on a 7-point rating scale, ranging from 1 (not at all) to 7 (very much) with a total score ranging between 5 and 35. The TCQ was administered for both aspects of the intervention: MBCT and mADM. Internal consistencies in the current study were α=.87 for the TCQ about MBCT and α=.85 for the TCQ about mADM. In the analyses, the difference between the credibility of MBCT and that of mADM (TCQ MBCT – TCQ mADM) was used as a predictor of treatment outcome, referred to as "MBCT preference strength".

2.5. Outcome measures

Adherence to MBCT included two aspects: the number of sessions attended and the average percentage of days per month at which patients practiced at home during the first three months. Home practice was assessed using calendars specifically designed for the study, on which participants could indicate their home practice (yes or no) on a daily basis.

Adherence to mADM also included two aspects: the dichotomous classification of using a therapeutic dose according to the Dutch pharmacotherapeutic compass (Health Insurance Board, 2000) at each follow-up contact during the observed time period (yes or no) and the average percentage of days per month at which patients used their medication during the first three months. This average percentage of medication use was calculated from the study calendars, on which patients indicated whether they had used medication (yes or no) on a daily basis, similar to the daily registration of mindfulness practice.

Primary outcome was relapse/recurrence as measured with the Structured Clinical Interview for DSM (SCID-I; First et al. (1996)) by trained research assistants every three months during the 15-month follow-up period. The interrater reliability between first and second (blind) ratings was found to be substantial (Kappa=0.70, $p < .001$, 95% CI 0.456–0.942).

Secondary outcomes were time to relapse/recurrence, the severity of depressive symptoms during follow-up and quality of life. The Inventory of Depressive Symptomatology – Clinician rated (IDS-C; Rush et al. (1996)) was used to assess severity of depressive symptoms at baseline, 3, 6, 9, 12 and 15 months. The IDS-C has good psychometric qualities (Rush et al., 1996; Trivedi et al., 2004). The internal consistency in the current study ranged between α=.85 and α=.92 across the six assessments. Quality of life was assessed at baseline, 3 and 15 months using the 26-item self-report WHOQOL short version (The WHOQOL Group, 1998). The WHOQOL assesses subjective quality of life in four domains: physical, psychological, social and environmental. Two questions with regard to overall perception of quality of life and health were included as well.

Table 1
Baseline demographic and clinical characteristics of patients with recurrent depression in remission participating in either trial A (MBCT preference; comparing MBCT+mADM versus MBCT alone) or trial B (mADM preference; comparing MBCT+mADM versus mADM alone).

Variable	(A) MBCT preference ($N=249$)		(B) mADM preference ($N=68$)		Comparison	
	N	%	*N*	%	χ^2	*p*
Female	168	67	49	72	0.52	.47
Educational level					3.68	.16
Low	17	7	8	12		
Middle	65	26	23	34		
High	154	62	35	51		
Missing	13	5	2	3		
Marital status					0.24	.89
Single	56	23	17	25		
Married/ cohabiting	141	57	40	59		
Divorced/ widowed	41	16	10	15		
Missing	11	4	1	1		
Employed	159	64	38	56	1.54	.22
Remission					0.63	.43
Full, IDS-C $\leq$ 11	133	53	40	59		
Partial, IDS-C > 11	116	47	28	41		
Type of mADM					0.32	.85
SSRI	190	76	51	75		
TCA	42	17	11	16		
Other[a]	17	7	6	9		
Previous CBT treatment	148	59	35	51	1.39	.24
Suicide attempt (lifetime)	47	19	11	16	0.27	.60
	Mean	SD	Mean	SD	*t*	*p*
Age (years)	50.3	10.6	51.8	14.2	−0.93	.35
Baseline depression (IDS-C)	12.6	10.0	12.1	9.6	0.34	.73
Nr. previous episodes	5.9	5.0	7.4	7.1	−2.02	.045
Age at MDD onset[b]	25.0	11.7	24.4	11.5	0.37	.71
MBCT preference strength[c]	1.4	5.8	−2.9	7.9	3.92	.00
Mindfulness skills (FFMQ)[d]	116.4	16.4	121.4	14.6	−2.22	.027

MBCT=mindfulness-based cognitive therapy; mADM=maintenance antidepressant medication; IDS-C=Inventory of Depressive Symptomatology – Clinician rated; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; CBT=cognitive-behavioural therapy; MDD=major depressive disorder; FFMQ=Five Facet Mindfulness Questionnaire.

[a] Including serotonin-norepinephrine reuptake inhibitors, monoamine oxidase-inhibitors, and mirtazapine.

[b] Based on self-report.

[c] Treatment Credibility Questionnaire (TCQ; Addis et al., 2004, Borkovec and Nau, 1972) was assessed twice: once for MBCT and once for mADM. Reported is the difference between these scores (TCQ MBCT – TCQ mADM), data available for $n=225$ in the MBCT preference group, and for $n=59$ in the mADM preference group.

[d] Total score, available for $n=228$ (MBCT preference group) and $n=64$ (mADM preference group).

2.6. Statistical analysis

All analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corporation, 2011) unless stated otherwise. Probability values lower than .05 (two-tailed) were considered significant for all analyses. Possible differences in baseline characteristics between participants with a preference for MBCT or mADM were examined using independent samples *t*-tests for continuous and Pearson χ^2 tests for categorical variables. For these analyses, we used data from the complete sample ($N=317$). For all other analyses we used the total number of patients who received MBCT and mADM ($N=154$). Analyses were based on intention-to-treat.

The association between preference type (MBCT versus mADM) and adherence to MBCT was examined with separate ANOVAs for (a) number of sessions and (b) percentage of home practice in the first three months. For MBCT preference strength as a predictor, we used linear regression analyses for (a) number of sessions and (b) amount of home practice, in separate analyses. The association between preference type (MBCT versus mADM) and adherence to mADM was examined with a Pearson Chi-square test (two-tailed) for the dichotomous adherence measure (yes or no) and ANOVA for the percentage of mADM adherence (days per month) in the first three months. MBCT preference strength was used as a predictor in a logistic regression model for the dichotomous measure and in a linear regression model for percentage adherence.

Relapse/recurrence rates in the two preference groups were compared with a Pearson χ^2 test and differences in time to relapse/recurrence were analysed using a Cox regression proportional hazards model. We used the same model to examine whether MBCT preference strength was a predictor of relapse risk. The severity of depression at baseline and the number of previous episodes (log transformed) were included as covariates because these factors have been consistently associated with an increased relapse risk (Hardeveld et al., 2010). In addition, we included baseline characteristics that were not balanced between the groups as covariates. Patients whose follow-up data were unavailable or who did not experience a relapse/recurrence before the end of the follow-up period were treated as censored observations.

The course of (residual) depressive symptoms (IDS-C) during the 15-month follow-up period was analysed using a latent growth curve model (LGCM) in MPlus version 7 (Muthén and Muthén, 1998) with 6 time points, a random intercept and a random slope for preference. To examine the predictive value of preference type and MBCT preference strength for symptom trajectory, both were added as covariates to the unconditional base model in separate analyses. In this way we could evaluate to what extent they predicted rate of change independent of initial level of depressive symptom severity. In both analyses, the number of previous episodes and mindfulness skills were included as covariates. Participants who did not complete all assessments were included in the analyses using full information maximum likelihood estimation for missing data.

Quality of life was analysed with a repeated measures ANOVA for both the observed dataset (complete case analysis) and the imputed dataset, using multiple imputation for missing data (Asendorpf et al., 2014).

3. Results

3.1. Patient preferences and associated factors

The flow of participants has been described in detail in the original publications (Huijbers et al., 2015; Huijbers et al., In press). As shown in Fig. 1, the majority of the included patients in both RCTs ($n=317$) preferred MBCT ($n=249$; 79%) and a minority preferred mADM ($n=68$; 21%). Table 1 shows the comparison of baseline demographic and clinical characteristics of those who preferred MBCT and those who preferred mADM. The group that preferred MBCT reported a higher MBCT preference strength (TCQ MBCT – TCQ mADM) than the mADM preference group (Cohen's $d=0.69$). The relation between preference type and MBCT preference strength is displayed in Fig. 2, showing that there was considerable variability in preference strength in both preference groups. Patients preferring mADM reported more previous episodes ($d=0.27$) and, interestingly, higher baseline levels of mindfulness skills ($d=0.31$). No other differences were found

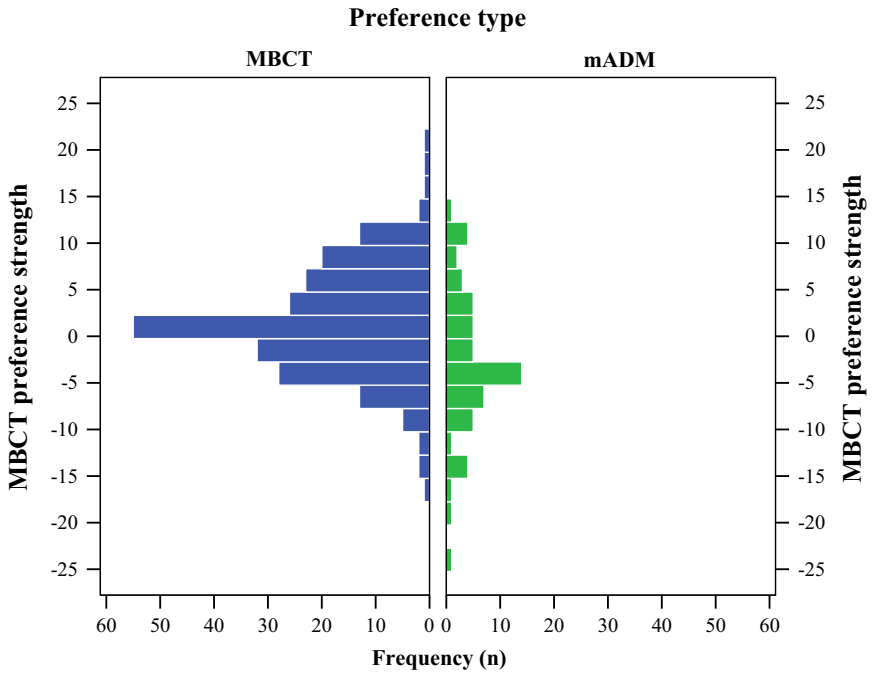

Fig. 2. The distribution of preference strength for mindfulness-based cognitive therapy (MBCT) over maintenance antidepressant medication (mADM) in patients preferring MBCT ($n=249$) and those preferring mADM ($n=68$). Distributions were similar for the subsample that was selected for the analyses of adherence and outcome.

between the groups.

3.2. Prognostic significance of preference type (MBCT versus mADM) and MBCT preference strength

3.2.1. MBCT adherence and mADM adherence

Table 2 shows the results for the comparisons between the preference groups for adherence to treatment. There were no differences between the groups on any of the included measures.

MBCT preference strength was not a predictor of the number of MBCT sessions attended ($\beta=-0.03$, $p=.70$) or the amount of home practice reported ($\beta=0.08$, $p=.42$). It did not predict adherence to mADM (odds ratio=0.95, 95% CI=0.89–1.01, $p=.10$) or the percentage of adherent days per month ($\beta=-0.15$, $p=.14$) either.

3.2.2. Primary outcome: relapse/recurrence of depression

No differences in relapse/recurrence rates were observed between the two preference groups. The relapse/recurrence rate was 39% (47/121) in the MBCT preference group and 36% (12/33) in the mADM preference group ($\chi^2=0.07$; $p=.80$).

As illustrated in Fig. 3, Cox regression analysis showed that preference for MBCT or mADM, corrected for baseline depression severity, number of previous episodes and mindfulness skills, did not predict the time to relapse/recurrence (hazard ratio=1.32, 95% confidence interval 0.70–2.51, $p=.41$).

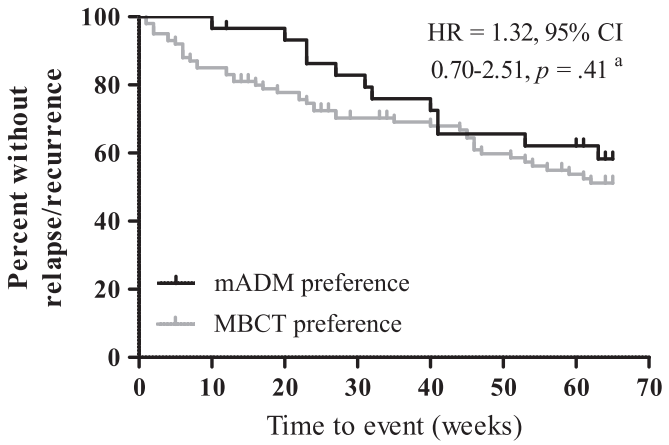

Fig. 3. Survival curves over 15-month follow-up (65 weeks) for the mindfulness-based cognitive therapy (MBCT) preference group ($n=121$) and maintenance antidepressant medication (mADM) preference group ($n=33$). [a] Using Cox regression analysis. HR=hazard ratio for MBCT preference compared to mADM; CI=confidence interval.

In addition, MBCT preference strength, corrected for baseline depression severity, number of previous episodes and mindfulness skills, did not predict time to relapse/recurrence either (hazard ratio=1.00, 95% confidence interval 0.97–1.05, $p=.85$).

Table 2
Comparisons between the MBCT preference and mADM preference groups for adherence to treatment.

	MBCT preference	*N*	mADM preference	*N*	Comparison
Adherence to MBCT					
Number of sessions; mean (SD), median	5.9 (2.6), 7	121	6.2 (2.5), 7	33	$F(1152)=0.45$, $p=.51$
Home practice, % of days per month; mean (SD)	0.83 (0.15)	79	0.82 (0.13)	26	$F(1103)=0.07$, $p=.80$
Adherence to mADM					
Adhered to protocol (yes/no); *N* (%)	87 (72)	121	28 (85)	33	$\chi^2=2.30$, $p=.13$
mADM use, % of days per month; mean (SD)	0.95 (0.01)	78	0.97 (0.02)	26	$F(1102)=1.54$, $p=.22$

MBCT=mindfulness-based cognitive therapy; mADM=maintenance antidepressant medication; SD=standard deviation.

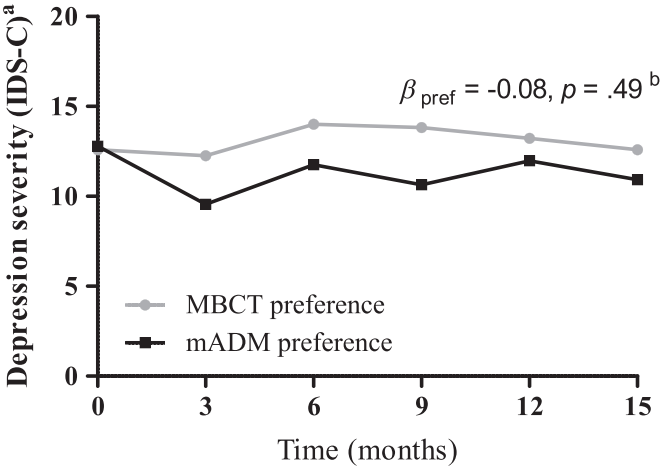

Fig. 4. Severity of (residual) depressive symptoms over 15-month follow-up for the mindfulness-based cognitive therapy (MBCT) preference group ($n=121$) and maintenance antidepressant medication (mADM) preference group ($n=33$). [a] IDS-C=Inventory of Depressive Symptomatology – Clinician Rated; cut-off points for depression severity: 0–11 none, 12–23 mild, 24–36 moderate, 37–46 severe, 47–84 very severe (Epidemiology Data Center, 2015). [b] Effect of preference group on the slope of depressive symptoms using a latent growth curve model.

3.2.3. Secondary outcomes: depression severity and quality of life

The latent growth curve analysis for severity of (residual) depressive symptoms (IDS-C) over the 15-month follow-up period showed an acceptable model fit for a linear growth model: comparative fit index=0.96, root mean square error of approximation=0.07, standardised root mean square residual=0.07. As shown in Fig. 4, patients more or less maintained mild levels of depression throughout the study period. Adding preference group, previous episodes, mindfulness skills, and intercept as predictors to the unconditional base model showed that the course of depression did not significantly vary between the preference groups ($\beta=-0.08$, se=.12, $p=.49$). In this analysis, 11 cases were excluded due to missing data on the covariates. Adding MBCT preference strength, previous episodes, mindfulness skills and intercept as predictors to the unconditional base model showed that the course of depression did not significantly vary with MBCT preference strength ($\beta=0.17$, se=.12, $p=.15$). Cases with missing data on any of the predictors were excluded from this analysis ($n=13$).

Table 3 shows the results for the analyses of quality of life. In summary, there were no differences between the preference groups with regard to quality of life.

4. Discussion

The current study investigated patients' treatment preferences for either MBCT or mADM to prevent relapse in recurrent depression, in two related RCTs. The majority of patients (79%) preferred trial A with MBCT in both study arms (MBCT+mADM or MBCT alone) over trial B with mADM in both study arms (MBCT+mADM or mADM alone). This finding is in accordance with previous studies indicating that most patients prefer psychological treatment or combined treatment over pharmacological treatment alone (Steidtmann et al., 2012; van Schaik et al., 2004).

Regarding baseline characteristics of patients with different types of treatment preferences, two previous studies suggested that patients with more severe depressive symptoms were more likely to prefer medication (Bedi et al., 2000; Dobscha et al., 2007). Although we did not replicate this finding in the current study, the higher number of previous episodes in the mADM preference group may indicate that patients with higher vulnerability for depression tend to stay on medication. Our finding that patients preferring mADM reported higher levels of mindfulness might indicate that they were more aware of, and more accepting towards their vulnerability for depression.

Looking at the group of participants who had been allocated to the combination of MBCT and mADM in both RCTs, patients with a preference for MBCT were not less adherent to mADM or more adherent to MBCT than those with a preference for mADM. Likewise, preference strength was not a predictor of adherence. Thus, our results are not in line with previous findings that preferences affect adherence and, consequently, internal study validity (Elkin et al., 1999; Iacoviello et al., 2007; Kwan et al., 2010; Raue et al., 2009). It is important to bear in mind, however, that despite differences in MBCT preference strength, patients in the mADM trial

Table 3
Quality of life at baseline, 3 and 15 months for the MBCT preference group ($n=121$) and mADM preference group ($n=33$), both receiving MBCT+mADM.

Variable	Baseline		3 months		15 months		p^a	p^b
	Mean (SD)	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*N*		
WHO-QoL – Q1: overall perception of quality of life							.71	.50
MBCT preference	3.5 (0.8)	113	3.6 (0.8)	86	3.7 (0.9)	68		
mADM preference	3.7 (0.7)	32	3.8 (0.7)	27	3.8 (0.8)	26		
WHO-QoL – Q2: overall perception of health							.53	.10
MBCT preference	3.4 (1.0)	113	3.3 (1.0)	85	3.4 (1.1)	68		
mADM preference	3.3 (0.9)	32	3.5 (1.1)	26	3.5 (0.9)	26		
WHO-QoL – physical domain							.87	.56
MBCT preference	24.2 (4.4)	113	24.6 (4.7)	86	25.6 (4.5)	67		
mADM preference	24.3 (3.3)	32	25.3 (3.9)	27	26.2 (4.2)	26		
WHO-QoL – psychological domain							.70	.36
MBCT preference	18.7 (3.2)	113	19.9 (3.6)	86	20.0 (3.8)	68		
mADM preference	19.3 (3.2)	32	20.5 (3.3)	27	20.2 (3.6)	26		
WHO-QoL – social domain							.47	.27
MBCT preference	9.8 (2.2)	113	10.0 (2.2)	86	10.1 (2.2)	68		
mADM preference	10.4 (2.4)	32	10.9 (1.9)	27	10.5 (2.5)	26		
WHO-QoL – environmental domain							.56	.44
MBCT preference	30.6 (4.0)	113	30.5 (4.2)	86	31.9 (4.0)	68		
mADM preference	31.2 (3.8)	32	30.4 (4.0)	27	31.6 (3.5)	26		

MBCT=mindfulness-based cognitive therapy; mADM=maintenance antidepressant medication; WHO-QoL=World Health Organisation Quality of Life.

[a] *p*-Value reported for the repeated measures analysis on preference – time interaction based on complete cases ($n=57$ MBCT preference and $n=24$ mADM preference).

[b] *p*-Value reported for the repeated measures analysis on preference – time interaction based on imputed data.

were also interested in mindfulness. The mADM preference group might represent a group of patients who are reluctant to discontinue their mADM, but actually willing to try MBCT as an add-on-treatment. This corresponds with previous findings that a large majority of patients preferred a combination of ADM and psychotherapy (Steidtmann et al., 2012). In addition, several patients allocated to mADM alone in trial B (Huijbers et al., 2015) did not adhere to the protocol: they participated in MBCT anyway. This points to the possibility that many patients actually preferred the combination treatment. Unfortunately we only asked patients' preferences for either MBCT or mADM, and not specifically for the combination therapy, MBCT alone or mADM alone.

Furthermore, preference type and strength of MBCT preference were not associated with treatment outcome. These findings correspond with previous studies comparing antidepressants and psychological interventions for MDD (Dunlop et al., 2012; Gelhorn et al., 2011) but contrast with the results of others (Raue et al., 2009; Swift et al., 2011). One explanation for our findings is that the subsample of patients in our outcome analyses was allocated to the combination of MBCT and mADM, which meant that they all received their preferred treatment. On the other hand, the key change from baseline was the addition of MBCT, as all patients were already using mADM for a longer period. Therefore, one would expect this addition of MBCT to be more beneficial for patients with a preference for it. The advantage of our approach is that patients were not demoralised by being allocated to a non-preferred treatment. The disadvantage, within the context of our research questions, is that the influence of patients' preferences may have been relatively small. In addition, different types of study design may lead to different results. For example, our study was different from most studies as our primary aim was prevention of relapse/recurrence. Given that patients were thus in remission at baseline, there was probably less room for improvement in terms of depression severity and quality of life as our secondary outcome measures. We cannot rule out the possibility that a preference for MBCT versus mADM would affect outcome in therapeutic studies. Nevertheless, the results of the current study suggest that the influence of preference on the internal study validity and outcome of MBCT (added to mADM) is limited.

This study provided a unique opportunity to investigate the impact of patient preference on the outcome of MBCT+mADM in remitted recurrently depressed patients. Patients from both preference groups were recruited in the same research sites and all assessments and interventions took place in the same way by the same people. Thus, the only apparent difference between them was their relative preference for MBCT or mADM. Of course, the comparisons that were made in the current study did not involve randomly allocated groups, so these groups did indeed differ for the number of previous episodes and level of mindfulness skills and may have differed in other aspects we did not assess. However, as the two preference groups did not differ on adherence or outcome, confounding factors explaining a possible difference are not particularly relevant. Furthermore, we used a clinician-rated instrument (IDS-C) to assess depression severity, which may be more objective than a self-report measure.

An important limitation of the current study is that the sample of patients with a preference for mADM was small. Hence, we may not have been able to detect possible differences between the groups. For example, there was some indication that patients in the mADM preference group were somewhat more likely to adhere to mADM (85%) compared with the MBCT preference group (72%). With the current sample size, we could have detected a difference of approximately 25% with 80% power. With the actual difference of 13%, the power was only 42%. Another limitation is that our study population probably consisted of a selected subsample of the larger population of patients with recurrent MDD. Patients not willing to take ADM at all, or those who had decided to withdraw from them before, were not part of our sample. Similarly, patients not interested in participating in MBCT will not have opted for the trial at all, so the study participants will have had a more than average interest in MBCT. As a consequence, it is likely that the difference in preference strength was relatively small in this study, compared to clinical practice. In patients with stronger and more specific preferences, for example for MBCT alone or mADM alone, the results of our comparison might have been different. Moreover, we cannot exclude the possibility that cultural or regional factors, such as attitudes towards MBCT or mADM, or availability of MBCT also influence patients' preferences. Hence, our results may only be generalisable to the Dutch mental health care system. It would be interesting to see whether our findings can be replicated in other countries.

The fact that we did not find an association between preference for either MBCT or mADM and treatment outcome is, in fact, pretty reassuring. Thus, patients who prefer to continue using their medication and who might not have high expectations from mindfulness may benefit to the same extent from MBCT as those who expect more. The current study also found no evidence for the idea that the internal validity had been affected by the patients' preference. That does not take away the fact that the external validity of the study may have been restricted by treatment preferences. We cannot extrapolate our findings to patients with stronger preferences for one of the monotherapies (i.e. MBCT without medication, or medication alone). For obvious reasons, it will not be easy if not impossible, to recruit these groups for future studies on treatment preference. It would nevertheless be interesting to include measures of patient preference in other studies of MBCT, where the design or population might be different.

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