BMJ Open

Discontinuing antidepressant medication after Mindfulness-Based Cognitive Therapy: A mixed-methods study exploring predictors and outcomes of different discontinuation trajectories, and its facilitators and barriers.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039053
Article Type:	Original research
Date Submitted by the Author:	02-Apr-2020
Complete List of Authors:	Huijbers, Marloes; Radboudumc, Psychiatry Wentink, Carolien; Radboudumc, Psychiatry Simons, Esther; Radboudumc, Primary and Community Care Spijker, Jan; Pro Persona Locatie Tarweweg, Expertise Centre for Depression Speckens, Anne; Radboudumc, Psychiatry
Keywords:	MENTAL HEALTH, PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, PUBLIC HEALTH, QUALITATIVE RESEARCH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE PAGE

Title:

Discontinuing antidepressant medication after Mindfulness-Based Cognitive Therapy: A mixed-methods study exploring predictors and outcomes of different discontinuation trajectories, and its facilitators and barriers.

Authors:

Marloes J Huijbers [1], Carolien Wentink [1], Esther Simons [2], Jan Spijker [3], Anne EM Speckens [1]*

[1] Department of Psychiatry, Radboud University Medical Centre, Nijmegen, the Netherlands

[2] Department of Primary and Community Care, Radboud University Medical Centre, Nijmegen, the Netherlands

[3] Pro Persona, Expertise Centre for Depression, Nijmegen, the Netherlands

*corresponding author due to maternity leave of Dr. M. Huijbers

Radboud University Medical Centre, department of Psychiatry

Reinier Postlaan 4, 6525 GC Nijmegen

The Netherlands

Tel: 0031-24-3668456

Email: Anne.Speckens@radboudumc.nl

Contact details M. Huijbers:

Tel: 0031-24-3610405

Email: marloes.huijbers@radboudumc.nl

Word count, excluding title page, abstract, references, figures, and tables: 3615.

ABSTRACT

Objectives

This study aimed to explore predictors and outcomes associated with different trajectories of discontinuing antidepressant medication (ADM), in recurrently depressed individuals after participation in Mindfulness-Based Cognitive Therapy (MBCT). Facilitators and barriers of discontinuation were explored qualitatively.

Design:

Mixed-methods study combining quantitative and qualitative data, drawn from a randomized controlled trial.

Setting: Twelve secondary and tertiary psychiatric outpatient clinics in the Netherlands.

Participants: Recurrently depressed individuals (N=226) who had been using ADM for at least six months and in partial or full remission. Regardless of trial condition, we made post-hoc classifications of patients' actual discontinuation trajectories: full discontinuation (n=82), partial discontinuation (n=34) and no discontinuation (n=110) of ADM within six months after baseline. A subset of patients (n=15) and physicians (n=7) were interviewed to examine facilitators and barriers of discontinuation.

Interventions: All participants were offered MBCT, which consisted of eight weekly sessions in a group.

Primary and secondary outcome measures: Demographic and clinical predictors of successful discontinuation within six months, relapse risk within 15 months associated with different discontinuations trajectories, and barriers and facilitators of discontinuation.

Results:

Of the 128 patients assigned to MBCT with discontinuation, only 68 (53%) fully discontinued ADM within 6 months, and 17 (13%) discontinued partially. Predictors of full discontinuation were female sex, being employed and lower levels of depression. Relapse risk was lower after no discontinuation (45%) or partial discontinuation (38%), compared with full discontinuation (66%) ($p = 0.02$). Facilitators and barriers of discontinuation were clustered within five themes: I) pre-existing beliefs about depression, medication and tapering; II) current experience with ADM; III) life circumstances; IV) clinical support; and V) mindfulness.

Conclusions:

Discontinuing antidepressants appears to be difficult, stressing the need to support patients and physicians in this process. MBCT may offer one of these forms of support.

Trial registration: ClinicalTrials.gov: NCT00928980. Post results.

Keywords antidepressants, discontinuation, recurrent depression, mindfulness-based cognitive therapy, barriers and facilitators

ARTICLE SUMMARY

Strengths and limitations of this study

- Rather than using opinions or hypothetical perspectives on tapering, this study used data on the actual discontinuation trajectories that recurrently depressed patients engaged in, and the associated predictors and outcomes.
- The facilitators and barriers reported by patients who attempted to discontinue are in accordance with and support previous findings from the qualitative literature.
- Professionals' perspectives were included to triangulate patients' perspectives on discontinuation of ADM in the qualitative study.
- Reports of relapse/recurrence may have been inflated by withdrawal or post-withdrawal symptoms, which could not be differentiated with the available data.
- Selection bias cannot be ruled out, as participation in the trial might have been influenced by perceptions and preferences regarding both mindfulness and the use of antidepressant medication.

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent mental disorder with a large burden of disease and high risk of recurrence.[1] One of the most commonly used and effective relapse prevention strategies is maintenance antidepressant medication (ADM), which seems more effective than placebo.[2] Current guidelines recommend patients with MDD to continue medication for at least two years after remission.[3 4] However, long-term use of ADM is often not preferred by patients due to side effects, pregnancy, or interaction with other medications, for example. As withdrawing from ADM can be associated with significant withdrawal effects,[5] and increased relapse risk,[6] there has been an upsurge in scientific and clinical attempts to improve discontinuations strategies.[7 8]

Psychological treatment strategies have been developed to protect against depressive relapse, among which Mindfulness Based Cognitive Therapy (MBCT).[9] A recent meta-analysis showed that MBCT is at least as effective in reducing the risk of depressive relapse/recurrence as maintenance antidepressants.[10] As MBCT provides patients support in the de-identification of thoughts and managing uncomfortable somatic sensations and emotions, it could also help patients to deal with possible withdrawal effects and increased emotional reactivity during discontinuation of ADM.[7 11]

Two randomized controlled trials (RCTs) in the UK, offering recurrently depressed patients MBCT with additional tapering support, indeed showed successful tapering of ADM in 75%[12] and 71% of their participants,[13] respectively. However, studies conducted in the Netherlands showed markedly lower levels of successful tapering, i.e. 53% when combined with MBCT,[6] less than 60% with Preventive Cognitive Therapy[14] and only 6% when tapering advise was given without further support.[15]

The aim of this study was to examine the predictors and outcomes of full, partial and no discontinuation of ADM, in recurrently depressed individuals who participated in MBCT in the context of an RCT.[6] In addition, we explored the barriers and facilitators of the discontinuation process by conducting in-depth qualitative interviews with a subsample of RCT participants and their attending clinicians.

METHODS

Data

Data originated from and RCT comparing MBCT followed by discontinuation or continuation of ADM.[6] For the current paper, groups were created post hoc based on patients' actual discontinuation profiles during the study, i.e. full, partial, or no discontinuation of their ADM. We invited a purposive sample of the participants and their attending clinicians for a semi-structured interview focussing on barriers and facilitators of discontinuation.

Participants

Patients with three or more previous depressive episodes who had been using ADM for 6 months or longer were recruited in 12 secondary and tertiary psychiatric outpatient clinics across the Netherlands between September 2009 and January 2012. The in- and exclusion criteria were described in full elsewhere. [6] The study was approved by the Medical Ethics Committee Arnhem-Nijmegen (nr. 2008/242).

Public and Patient Involvement

During the entire study period of the RCT from which these data were drawn, patients and health care professionals in the participating centres were informed about the progress of the study, and later on about its results, via newsletters every quarter. The qualitative data presented in the current study are in itself a reflection of patients' and professionals' perspective on the topic. In addition, the qualitative feedback on the barriers and facilitators of MBCT as supportive intervention during discontinuation of ADM has been directly translated into the refinement of an MBCT intervention to support ADM discontinuation, investigated in an RCT conducted between 2015 and 2019 by our group.[16]

Procedure

A detailed description of the study procedures in line with CONSORT guidelines is provided in the RCT report.[6] Eligible patients were randomly assigned to MBCT followed by guided discontinuation of ADM or to MBCT with continuation of ADM. Follow-up assessments took place 3, 6, 9, 12, and 15 months after baseline.

For the qualitative part of the study, we adhered as much as possible to the Standards for Reporting Qualitative Research (SRQR).[17] A subset of 15 participants from the MBCT+Discontinuation group were purposively sampled on the basis of age, sex, and discontinuation profile. We kept inviting participants until saturation of the data was established. For the purpose of triangulation, we also included physicians who had guided discontinuation. Interviews were semi-structured, individual and by telephone. Patients and attending physicians were asked the following questions: 1) "What hampered your (the patients') discontinuation process?"; 2) "What facilitated your (the patients') discontinuation process?"; and 3) "What was the role of mindfulness in your (the patients') process of discontinuation?". The interviews were conducted by CW and ES, both female. CW was a psychologist and PhD student on a project investigating ADM discontinuation in primary care. ES was a medical student completing her research internship. Neither of them were acquainted with the participants prior to the interviews.

Interventions

Mindfulness-Based Cognitive Therapy (MBCT)

MBCT was largely based on the protocol by Segal, Williams, and Teasdale[9] and consisted of eight weekly sessions of 2.5 hours and one day of silent practice between the sixth and seventh session. It was delivered in groups of eight to 12 participants and included mindfulness meditation practices, group inquiry, cognitive-behavioural elements, interactive psycho-education, and home practice.

Discontinuation or continuation of ADM

Patients in the discontinuation arm were asked and recommended to gradually withdraw from their ADM over a period of five weeks, starting after the seventh session of MBCT, with specified steps for each of the commonly used types of antidepressants[18] and supervised by their attending physician (mostly psychiatrists) in three to 12 consultations. Patients in the continuation arm were offered a minimum of one consultation. Psychiatrists were instructed to maintain or reinstate an adequate dose of ADM, and recommendations to manage side effects were provided. Full discontinuation was defined as tapering to nil milligrams within six months after baseline. Partial discontinuation was defined as tapering to a lower dose and 'no discontinuation' was defined as maintaining or increasing the initial therapeutic dose of ADM throughout the first six months after baseline.

Outcome measures

Relapse/recurrence rates were compared between the three discontinuation subgroups (full, partial, not). It was assessed using the Structured Clinical Interview for DSM-IV[19] (SCID) 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). Baseline severity of depressive symptoms was measured with the Inventory for Depressive Symptomatology (IDS-C).[20]

Statistical and qualitative analysis

All analyses were performed using SPSS Statistics version 20.0. Probability values lower than 0.05 (two-tailed) were considered significant for all analyses. Possible differences in baseline characteristics between participants who discontinued fully, partially or not at all were examined using independent samples t-tests for continuous and Pearson χ^2 tests for categorical variables.

Relapse/recurrence rates across the entire trial sample, differentiated into three discontinuation profile groups (full, partial, not) were compared with a Pearson χ^2 test and differences in time to relapse/recurrence were analysed using a Cox regression proportional hazards model. Baseline depression severity and number of previous episodes (log transformed) were included as covariates because these factors have been consistently associated with an increased relapse risk.[21] 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.

Qualitative The qualitative interviews were audio-taped, transcribed verbatim en imported in the scientific qualitative research software program ATLAS.ti (version seven). The constant comparative method was used to analyze the data.[22] Analysis started as soon as the first data were collected and continued with each additional interview. Two researchers (CW, ES) coded the transcripts independently to minimize subjectivity. Subsequently codes were modified and categorized as themes related to facilitators and barriers. These were discussed by the researchers with the supervisors, AS and MH. AS was a professor of psychiatry and mindfulness teacher with prior experience with qualitative research. MH was a psychologist and post-doc researcher. Characteristic quotes were used to illustrate the findings. The original Dutch quotes in this article were translated into English by the authors.

RESULTS

Quantitative results

Flow of ADM discontinuation and intervention adherence

The flow of participants and their ADM use is shown in Figure 1. Of the 249 participants randomized, 128 were allocated to MBCT+Discontinuation and 121 to MBCT+ADM. From 23/249 (9%) patients, we had insufficient information about ADM use due to early dropout. Consequently, descriptive and statistical analyses were performed on 226 participants.

Of the 82 patients who fully discontinued ADM within six months after baseline, 41 (50%) restarted ADM at some point during the 15-month study period. Based on the SCID interviews, this might have been related to a relapse in 31/41 (76%) of them.

Adherence to MBCT sessions differed significantly among the three groups: M=7.2 ± 1.5 for those with a full discontinuation profile, M=7.0 ± 1.4 for partial discontinuation, and M=6.4 ± 2.0 for the no discontinuation group. The number of medication consultations also differed significantly among the three groups, being highest for those with a full discontinuation profile (M=3.0 ± 2.0; range 0-13) versus partial discontinuation (M=2.3 ± 1.4; range 1-6) versus no discontinuation group (M=1.6 ± 1.5; range 0-11).

[Figure 1]

Demographic and clinical characteristics

The demographic and clinical characteristics for the different profile groups are summarized in Table 1. In comparison with those who did not discontinue, females were more likely to fully discontinue than men (76% versus 53%; p = 0.026) and employed participants more likely than those who were unemployed (78% versus 56%; p = 0.002). Those who fully discontinued also had significantly less depressive symptoms at baseline than those who did not (M=10.9 (SD 8.8) vs M=14.4 (SD 10.6), p = 0.018; d = 0.37).

Table 1. Baseline demographic and clinical characteristics of 226 patients with recurrent depression receiving mindfulness-based cognitive therapy who subsequently engaged in full, partial, or no discontinuation of maintenance antidepressant medication (adapted from Huijbers et al, 2016).

	Total N = 226 [a]						
Variable	**Full discontinuation (n = 110)**		**Partial discontinuation (n = 34)**		**No discontinuation (n = 82)**		**Sig.**
	N	%	N	%	N	%	*p*
Female	62	76	18	53	71	64	**0.048**
Educational level							0.421

-Low	7	9	3	9	6	6	
-Middle	24	29	10	29	31	28	
-High	49	60	21	62	64	58	
-Missing	2	2	0	0	9	8	
Marital status							0.560
-Single	19	23	6	18	27	25	
-Married/cohabiting	46	56	22	65	60	55	
-Divorced/widowed	15	18	6	18	16	15	
-Missing	2	2	0	0	7	6	
Employed (n=225)	63	78	22	65	62	56	**0.009**
Remission							0.069
-Full, IDS-C ≤ 11	51	62	17	50	50	45	
-Partial, IDS-C > 11	31	38	17	50	60	55	
Type of mADM							0.669
-SSRI	64	78	23	68	21	19	
-TCA	13	16	7	21	21	19	
-Other [b]	5	6	4	12	6	6	
Previous CBT treatment	45	55	21	62	68	62	0.595
Suicide attempt (lifetime)	18	22	12	15	21	49	0.429
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	50.0	11.1	52.0	9.8	51.0	10.3	0.507
Baseline depression (IDS-C)	10.9	8.8	12.7	11.2	14.4	10.6	0.059
Nr. previous episodes	5.6	4.9	7.4	8.0	5.7	3.9	0.167
Age at MDD onset (n=219)	27	11.9	25	10.8	25.0	12.3	0.388

Legend: IDS-C, Inventory of Depressive Symptomatology – Clinician rated; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; CBT, cognitive-behavioural therapy; MDD, major depressive disorder.

[a] Excluding 23 of the original 249 trial participants due to missing data regarding discontinuation.

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

Relapse and recurrence

Rates of relapse were 66% for full discontinuation, 38% for partial discontinuation and 45% for no discontinuation. As illustrated in Figure 2, Cox regression analysis with baseline level of depression and number of previous episodes (log transformed) as covariates showed that there were significant differences in terms of risk of relapse across the three groups (p = 0.02). Compared with the full discontinuation group, those who did not discontinue had a lower risk of relapse (hazard ratio = 0.67; 95% CI = 0.45 – 0.99; p = 0.04). The lowest risk of relapse was seen for those who partially

discontinued, compared with full discontinuation (hazard ratio = 0.47; 95% CI = 0.26 – 0.87; p = 0.02). There was no significant difference in relapse risk between partial and no discontinuation (p = 0.27).

[Figure 2]

Qualitative results

The interviewed patients consisted of eight women and nine men, with a mean IDS-score at baseline of 11 ± 7.8. See Table 2 for their characteristics. Nine patients discontinued their ADM fully, three partially and three did not discontinue their ADM.

Table 2. Patients' characteristics for the subset of participants in the qualitative study.

Patient	Sex	Age	IDS at baseline	Discontinuation ≤6 months	Relapse ≤15 months
P1	male	39	9	Partially	No
P2	male	45	15	Not	No
P3	female	33	10	Fully	Yes
P4	female	23	10	Fully	Yes
P5	male	68	0	Fully	Yes
P6	female	50	13	Partially	Yes
P7	male	71	10	Fully	No
P8	female	50	17	Partially	Yes
P9	male	53	3	Not	Yes
P10	male	60	30	Fully	Yes
P11	female	62	20	Not	Yes
P12	female	57	7	Fully	Yes
P13	male	58	14	Fully	No
P14	female	35	14	Fully	Yes
P15	female	68	0	Fully	No

Five themes emerged from the patient interviews: I) patients' pre-existing beliefs about depression, medication and tapering; II) current experience with antidepressants; III) psychosocial conditions and

physical problems; IV) clinical support and V) participating in MBCT. The most significant subthemes are described in more detail below. See online supplement 1 for an overview of themes, subthemes and illustrating quotes.

I. Pre-existing beliefs about depression, medication and tapering

Facilitators

Being aware that others are also subject to periods of low mood and feeling downhearted occasionally seemed to facilitate the process of discontinuation. This was accompanied by the realization that medication is not always needed to suppress those feelings. Although most respondents had regarded their medication as helpful during their depression, some patients considered taking pills for long periods of time as unhealthy and even 'harmful'. Respondents also talked about their wish to manage without pills.

Barriers

Several respondents mentioned that they were (told to be) missing a specific substance in their brain and therefore needed ADM. They considered their condition as chronic and medication as necessary. Not surprisingly, these people were reluctant to (fully) taper their medication. Another central theme was the fear of relapse in depression. Several patients expressed concern that this would happen. On a related note, many participants had tried to come off medication in the past and experienced difficulties, i.e. withdrawal symptoms.

II. Current experience with antidepressants

Facilitators

There were patients describing uncertainty about the benefits of taking their medication. In addition, the occurrence of unwanted or 'side' effects emerged as a theme. In addition, being able to adopt a personalized tapering schedule facilitated the discontinuation process. Such a personalized schedule

typically contained adaptations with regard to the duration and magnitude of the dose reductions, or were much more flexible so that tapering could be guided by their own mental health state.

Barriers

Some participants for whom ADM were still beneficial in managing depressive symptoms did not start discontinuation. Withdrawal effects appeared one of the major reasons to interrupt discontinuation, restart or increase the dose of medication. For many patients the tapering speed according to the RCT guideline was considered too fast.

III. Life circumstances

Facilitators

In a relatively quiet period, people appeared more likely to start and proceed with tapering.

Barriers

If there were stressful circumstances (for example, work-related problems), a lack of support from family or friends, or health problems, people seemed more reluctant to start or continue the tapering process.

IV Clinical support

Facilitators

Availability and accessibility of professional guidance was an important facilitator, both before and during the tapering process. Patients mentioned the importance of bringing in their own ideas of how clinical support would ideally look like, and having the freedom to choose for themselves what they felt was best. Reassurance about being able to restart medication in case of deterioration was also described as helpful.

Barriers

In some cases the attending clinician would advise against discontinuation, which was mentioned as a barrier. Another barrier that emerged from the interviews was the impression that, possibly related to the context of the RCT, tapering was mandatory.

V. Mindfulness practice

Facilitators

Participants mentioned peer support in MBCT as a facilitating factor. Witnessing how other people deal with similar problems and sharing fears and insecurities about tapering were regarded as helpful and reassuring. In addition, mindfulness itself had been a source of support during tapering, for example being able to distinguish feelings of stress from a depressive relapse and recognizing that these were triggered by difficult psychosocial circumstances, which did not necessarily require to restart medication. Mindfulness practice also provided an alternative method to prevent depressive relapse, by recognizing periods of increased vulnerability and using other approaches rather than increasing the dose of ADM (e.g. daily walks in nature, seeing friends and reducing workload).

Barriers

The MBCT group context could also negatively impact the process. MBCT groups included participants from both arms of the RCT, including those who were asked to continue ADM after MBCT. It was mentioned that sometimes fellow group members, who continued their medication, advised against discontinuation.

Facilitators and barriers as reported by attending clinicians

Fourteen patients gave permission to interview their attending physician, of whom seven were willing and able to participate. See Table 3 for their characteristics.

Table 3. Professionals' characteristics.

Professional	Sex	Age	Function	Institute
PF1	female	54	psychiatrist	university medical center
PF2	female	30	psychiatrist in training	university medical center
PF3	female	41	psychiatrist	mental health institute
PF4	female	48	physician	university medical center
PF5	male	63	psychiatrist	private practice
PF6	female	51	psychiatrist	university medical center
PF7	male	47	psychiatrist	mental health institute

Professionals' perspectives generally showed a large overlap with the views expressed by participants. For example, the benefits of tapering slowly and with a personalized tapering scheme clearly emerged from these interviews. In terms of barriers, the pivotal roles of negative experiences with tapering in the past, worrying about symptoms and possible relapse, and stressful circumstances were mentioned.

Some different themes emerged from these interviews as well. Clinicians reported feeling reluctant to discontinue ADM because of their own worries about patients having a relapse, especially in case of a long psychiatric history or comorbidity. They spoke more specifically about ADM characteristics (half-life time) and switching to a different type of ADM before fully discontinuing as a possible facilitator. They also mentioned the possible use of other psychological interventions to help patients cope with emerging symptoms. Regarding barriers, clinicians were particularly concerned about nocebo effects when discussing potential withdrawal effects, suggesting to provide some information but avoiding being very specific about it.

DISCUSSION

Principal findings

The current paper provides quantitative post-hoc data from an RCT, describing the flow, characteristics and outcomes of patients with recurrent depression who discontinued ADM fully, partially or not at all. Quantitative data were complemented by qualitative data on the barriers and facilitators of ADM withdrawal. In the original MBCT+discontinuation treatment arm, only 53% of the participants were able to fully discontinue within six months from baseline, 13% discontinued partially and 25% of the participants decided to continue their medication as it was despite the randomization. Notably, discontinuation also occurred in patients asked to continue their medication: 12% discontinued fully and 14% partially. These non-compliance rates and apparent difficulties with discontinuation are in line with previously published studies on (preventive) cognitive therapy for recurrently depressed patients[23] and anxiety disorders.[24]

Full discontinuation occurred more frequently in women, and in those who were employed. Indeed, the qualitative data point to psychosocial stressors as possible barriers to discontinuation, and problems with finding or holding on to a suitable job might be one of them. In addition, tapering appeared more feasible for those with lower levels of baseline depression. In contrast, the qualitative data suggest that if ADM are considered an effective treatment to reduce or manage depressive symptoms, patients are *less* likely to taper, and vice versa. Possibly, these beliefs may vary over time and across circumstances. For example, a patient who considers tapering because ADM has not been very effective, but would nevertheless postpone this because of a current episode of depression.

Even in those participants who discontinued completely in the current study, more than half restarted medication within the next nine months, possibly related to relapse or recurrence of depression. Relapse rates were indeed substantially higher for fully discontinued patients than for partially and not discontinued. These differences seem clinically relevant, and may even advocate partial rather than full discontinuation. While linear tapering regimes are commonplace, the most challenging part of the withdrawal process may occur at the lowest doses. As this might have to do with hyperbolic dose-response relationships between drugs such as selective serotonin reuptake inhibitors and their receptor,[25] it has been suggested that “stop slow if you go low” regimes may help to minimize withdrawal symptoms.[26] Although the use of “tapering strips” can be a suitable way to taper gradually,[27] for many types of ADM these are not yet available.

In line with a recent systematic review,[28] worry and fear of relapse emerged as clear barriers to discontinuation in the qualitative interviews. These fears appear to exist not only for patients, but also for attending physicians. Some professionals reported being anxious about responsibility for deterioration and sometimes feeling unable to help, which has also been reported in previous studies.[29] For both patients and professionals, accessibility and availability of support during tapering is important.

Strengths and weaknesses

A major strength of the current study is that we combined quantitative and qualitative data to investigate what makes it more difficult or easy to discontinue ADM. Rather than using opinions or hypothetical perspectives on tapering, we report data on the actual tapering process in an RCT, including clinical outcomes. In addition, we looked at professionals' perspectives to triangulate patients' perspectives on discontinuation of ADM in the qualitative study.

One of the limitations of the current study is that reports of relapse/recurrence may have been inflated by withdrawal or post-withdrawal symptoms. Chouinard and Chouinard have developed criteria permitting identification of three types of withdrawal problems associated with SSRIs: new withdrawal symptoms, rebound and persistent post withdrawal disorder, which can be differentiated from relapse and recurrence.[30] As withdrawal symptoms were not included as an outcome measure, we could unfortunately not differentiate this in our RCT.

Another limitation is that we cannot rule out selection bias, as participation in the trial might have been influenced by perceptions of both mindfulness and ADM. Participants in the qualitative part of the study may be more positive about MBCT than those who dropped out of the intervention. In addition, the number of professionals contributing to the qualitative interview data was rather small.

Clinical recommendations

First and foremost, our findings clearly point to the necessity of up-to-date, accessible and professional guidance for those who wish to come off their ADM. A recently published shared decision making tool[31] might assist patients and their clinicians in their consultations. Secondly, a personalized tapering approach seems essential to enable successful tapering. With accumulating evidence suggesting that slow tapering is associated with better outcomes,[32] it is important to slow down the pace of tapering on the basis of patients' preferences and needs. Finally, results from the current study point to the possible clinical relevance of tapering to low doses of ADM rather than complete withdrawal. This might prevent withdrawal symptoms, whether neurochemical or psychological, empower patients by letting them choose their optimal dose, and reduce side effects and health care costs.

Research implications

So far, it remains unclear whether the increased risk of relapse and withdrawal symptoms are a direct effect of neurobiological changes, or an indirect effect driven by psychological mechanisms such as fear of relapse, negative expectations based on previous failed tapering attempts, or nocebo effects caused by information about withdrawal symptoms. To disentangle these effects at a more fundamental level, a double-blind withdrawal study with active versus placebo pills should be conducted.

In addition, future research might focus on the effectiveness of protocolized tapering support interventions and existing psychological interventions that might be helpful to manage withdrawal symptoms and depression. Besides MBCT, Preventive Cognitive Therapy might be a valuable option.[14] Future studies should include homogeneous groups of patients who are all in the same phase of discontinuation. We are currently conducting an RCT in primary care inviting long-term ADM users who have made a shared decision to discontinue, are supported by mental health assistants or their GP in devising and monitoring their tapering process, and are either offered additional MBCT or not.[16]

Funding statement

The RCT from which data were drawn was funded by ZonMW, the Netherlands Organization for Health Research and Development (Grant no. 170992903 awarded to Prof. A.E.M. Speckens). No additional funding was requested for the current mixed-methods study. The funder had no role in the writing of the manuscript or the decision to submit it for publication.

Data sharing

We aim to make our data available for other researchers as much as possible, albeit with a restricted access policy. As data are currently not yet filed in a public repository, researchers interested in re-using our data are invited to contact the authors.

Competing interests

MH and AS report grants from ZonMW Doelmatigheid, during the conduct of the study; CW, ES and JS have nothing to disclose.

Author contributions

MH and AS led the RCT from which the quantitative data were drawn. For the current study, MH, CW, JS and AS formulated the study design. MH and CW collected data. ES assisted with data collection. MH and CW contributed to data analysis and data interpretation. MH wrote the manuscript and prepared the figures and tables. CW, ES, JS and AS edited the manuscript.

Acknowledgements

The authors would like to acknowledge all participants who have contributed to this work, as well as all health care professionals who have participated in the trial and those who contributed to the qualitative interviews.

REFERENCES

1. Richards D. Prevalence and clinical course of depression: a review. *Clinical psychology review* 2011;31(7):1117-25. doi: 10.1016/j.cpr.2011.07.004 [published Online First: 2011/08/09]
2. Gueorguieva R, Chekroud AM, Krystal JH. Trajectories of relapse in randomised, placebo-controlled trials of treatment discontinuation in major depressive disorder: an individual patient-level data meta-analysis. *The lancet Psychiatry* 2017;4(3):230-37. doi: 10.1016/s2215-0366(17)30038-x [published Online First: 2017/02/13]
3. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (3rd ed.): APA, 2010.
4. National Institute for Health and Care Excellence. Depression in adults: recognition and management. CG90. London: NICE, 2009.
5. Davies J, Read J. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? *Addictive behaviors* 2019;97:111-21.
6. Huijbers MJ, Spinhoven P, Spijker J, et al. Discontinuation of antidepressant medication after mindfulness-based cognitive therapy for recurrent depression: randomised controlled non-inferiority trial. *British Journal of Psychiatry* 2016;208(4):366-73. doi: 10.1192/bjp.bp.115.168971
7. Maund E, Stuart B, Moore M, et al. Managing Antidepressant Discontinuation: A Systematic Review. *Annals of family medicine* 2019;17(1):52-60. doi: 10.1370/afm.2336 [published Online First: 2019/01/24]
8. Bowers HM, Kendrick T, Glowacka M, et al. Supporting antidepressant discontinuation: the development and optimisation of a digital intervention for patients in UK primary care using a theory, evidence and person-based approach. *BMJ Open* 2020;10(3):e032312. doi: 10.1136/bmjopen-2019-032312 [published Online First: 2020/03/11]
9. Segal, Williams JMG, Teasdale JD. Mindfulness-Based Cognitive Therapy for Depression, 2nd edn.: Guilford Press 2012.
10. Kuyken W, Warren FC, Taylor RS, et al. Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse: An Individual Patient Data Meta-analysis From Randomized Trials. *JAMA Psychiatry* 2016;73(6):565-74. doi: 10.1001/jamapsychiatry.2016.0076 [published Online First: 2016/04/28]
11. Tickell A, Byng R, Crane C, et al. Recovery from recurrent depression with mindfulness-based cognitive therapy and antidepressants: a qualitative study with illustrative case studies. *BMJ Open* 2020;10(2):e033892. doi: 10.1136/bmjopen-2019-033892 [published Online First: 2020/02/23]
12. Kuyken W, Byford S, Taylor RS, et al. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. *J Consult Clin Psychol* 2008;76(6):966-78. doi: 10.1037/a0013786 [published Online First: 2008/12/03]
13. Kuyken W, Hayes R, Barrett B, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. *Lancet (London, England)* 2015;386(9988):63-73. doi: 10.1016/s0140-6736(14)62222-4 [published Online First: 2015/04/25]
14. Bockting CL, Klein NS, Elgersma HJ, et al. Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. *The Lancet Psychiatry* 2018;5(5):401-10.
15. Eveleigh R, Muskens E, Lucassen P, et al. Withdrawal of unnecessary antidepressant medication: a randomised controlled trial in primary care. *BJGP Open* 2018;1(4):bjgpopen17X101265.
16. Wentink C, Huijbers MJ, Lucassen P, et al. Discontinuation of antidepressant medication in primary care supported by monitoring plus mindfulness-based cognitive therapy versus

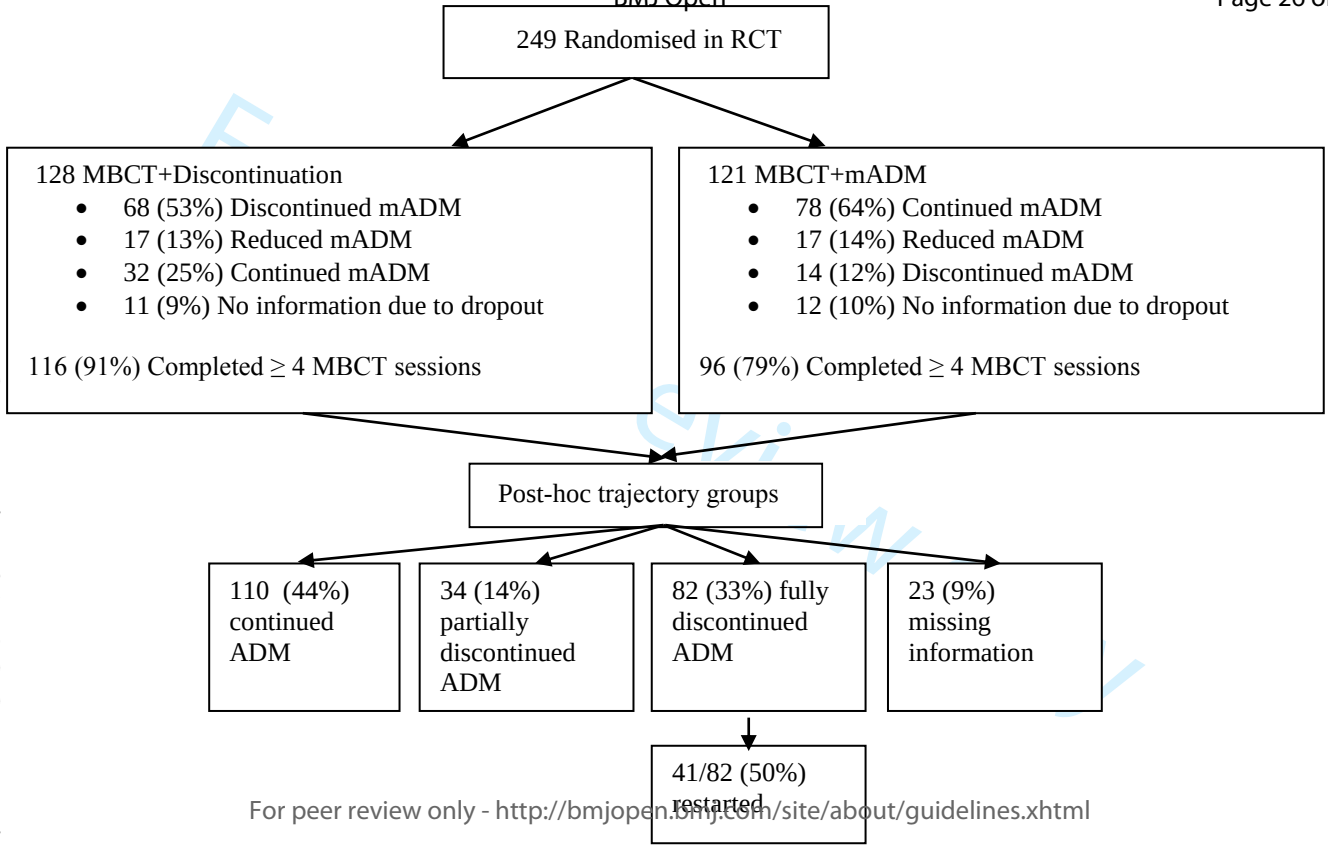
monitoring alone: design and protocol of a cluster randomized controlled trial. *BMC family practice* 2019;20(1):105.
17. O'Brien BC, Harris IB, Beckman TJ, et al. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med* 2014;89(9):1245-51. doi: 10.1097/acm.0000000000000388 [published Online First: 2014/07/01]
18. Huijbers MJ, Spijker J, Donders AR, et al. Preventing relapse in recurrent depression using mindfulness-based cognitive therapy, antidepressant medication or the combination: trial design and protocol of the MOMENT study. *BMC Psychiatry* 2012;12(1):125. doi: 10.1186/1471-244x-12-125 [published Online First: 2012/08/29]
19. First MB, Gibbon M, Spitzer RL, et al. User's guide for the structured clinical interview for DSM-IV axis I Disorders—Research version. *New York: Biometrics Research Department, New York State Psychiatric Institute* 1996
20. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): Psychometric properties. *Psychol Med* 1996;26(3):477-86.
21. Hardeveld F, Spijker J, De Graaf R, et al. Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatr Scand* 2010;122(3):184-91. doi: 10.1111/j.1600-0447.2009.01519.x [published Online First: 2009/12/17]
22. Boeije H. A purposeful approach to the constant comparative method in the analysis of qualitative interviews. *Quality and quantity* 2002;36(4):391-409.
23. Bockting CLH, Klein NS, Elgersma HJ, et al. Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. *The lancet Psychiatry* 2018;5(5):401-10. doi: 10.1016/s2215-0366(18)30100-7 [published Online First: 2018/04/08]
24. Scholten WD, Batelaan NM, van Oppen P, et al. The Efficacy of a Group CBT Relapse Prevention Program for Remitted Anxiety Disorder Patients Who Discontinue Antidepressant Medication: A Randomized Controlled Trial. *Psychotherapy and psychosomatics* 2018;87(4):240-42. doi: 10.1159/000489498 [published Online First: 2018/06/04]
25. Meyer JH, Wilson AA, Sagrati S, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. *Am J Psychiatry* 2004;161(5):826-35. doi: 10.1176/appi.ajp.161.5.826 [published Online First: 2004/05/04]
26. Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. *The lancet Psychiatry* 2019;6(6):538-46. doi: 10.1016/s2215-0366(19)30032-x [published Online First: 2019/03/10]
27. Groot PC, van Os J. Antidepressant tapering strips to help people come off medication more safely. *Psychosis* 2018;10(2):142-45. doi: 10.1080/17522439.2018.1469163
28. Maund E, Dewar-Haggart R, Williams S, et al. Barriers and facilitators to discontinuing antidepressant use: A systematic review and thematic synthesis. *Journal of affective disorders* 2019;245:38-62. doi: 10.1016/j.jad.2018.10.107 [published Online First: 2018/10/27]
29. Bowers HM, Williams SJ, Geraghty AWA, et al. Helping people discontinue long-term antidepressants: views of health professionals in UK primary care. *BMJ Open* 2019;9(7):e027837. doi: 10.1136/bmjopen-2018-027837 [published Online First: 2019/07/07]
30. Chouinard G, Chouinard VA. New Classification of Selective Serotonin Reuptake Inhibitor Withdrawal. *Psychotherapy and psychosomatics* 2015;84(2):63-71. doi: 10.1159/000371865 [published Online First: 2015/02/28]
31. Wentink C, Huijbers MJ, Lucassen PLBJ, et al. Enhancing shared decision making about discontinuation of antidepressant medication: a concept-mapping study in primary and secondary mental health care. *British Journal of General Practice* 2019 doi: 10.3399/bjgp19X706001

32. Baldessarini RJ, Tondo L, Ghiani C, et al. Illness risk following rapid versus gradual discontinuation of antidepressants. *The American journal of psychiatry* 2010;167(8):934-41. doi: 10.1176/appi.ajp.2010.09060880 [published Online First: 2010/05/19]

Figure captions

Figure 1. Flow chart of participants, their adherence to mindfulness-based cognitive therapy (MBCT) and their use of antidepressant medication (ADM).

Figure 2. Survival curves over 15-month follow up for risk of relapse in recurrently depressed patients with different profiles of discontinuing antidepressant medication: fully (n=82), partially (n=34) or not (n=110).



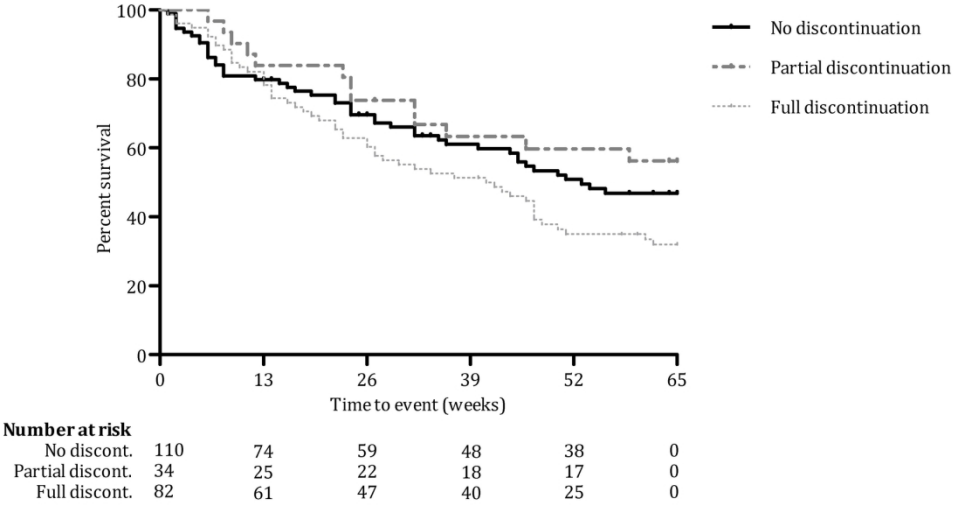


Figure 2. Survival graph.

169x94mm (300 x 300 DPI)

Online supplement 1. Facilitators and barriers in the discontinuation of antidepressant medication as experienced by patients with recurrent depression who had participated in an MBCT course. Most subthemes are illustrated with quotes in italic.

THEMES	FACILITATORS TO DISCONTINUATION	BARRIERS TO DISCONTINUATION
I Pre-existing beliefs		
About depression	Common humanity *"I noticed that I, well, that I am not always feeling that cheerful. And I have accepted myself as such by now, this is who I am" (woman, 50, partially discontinued)*	Missing substance in the brain
About medication	ADM as harmful *"Yes actually I wanted to get rid of that junk. I call it junk now, but of course it is a beautiful invention, glad that it exists, but I still think .. well, if I can do it without pills." (man, 53, not discontinued)* Dependency as weakness *"I want to be able to do it myself. It also felt somewhat like a weakness, that you would need a pill to feel reasonably well" (woman,23, fully discontinued)*	Accepting long-term use *"At a certain moment I thought well, life without medication, well for some people this could be an option I guess, but not for me." (man, 39, partially discontinued)*
About tapering	Open mind	Fear of relapse in depression *"That you relapse into a more severe depression than before (..) And I have had such an experience and did not want to go through that again." (woman, 50, partially discontinued)* Previous negative experiences with withdrawal effects during tapering

II. Current experience with antidepressants		
Effectiveness	ADM does not help (anymore) *"… the idea that those things are not helping me anyway. I thought well, I am taking poison, and it doesn't really help."* (man, 68, fully discontinued)	ADM (still) works for me
Side effects	Side effects when using ADM *"Because I feel that my memory has gotten really worse. And when I was still fully on medication I noticed that my hands were just trembling a lot, and well.. I regarded that as a very bad sign (..) so I thought, I have to get rid of that."* (woman, 50, partially discontinued)	
Withdrawal effects		Withdrawal effects *"I was using Citalopram and I believe I had to taper within 2 weeks, but I was suffering quite a lot from withdrawal symptoms, so therefore, after consultation, tapered somewhat more slowly."* (woman, 23, fully discontinued)
Tapering schedule	Individual, step by step	Too fast and/or steps too big *"And then it was advised to taper within 6 months, I discussed that with my doctor and he was not very keen on that and I thought I do not want to fall back again as I had done before. So for sure I am not going to taper as fast as the six months they suggested."* (woman, 50, partially discontinued)

III. Life circumstances		
Psychosocial conditions	Relatively quiet period *"Just a quiet period so I thought I could put it to the test." (man, 68, fully discontinued)*	Social stressors *"I had just divorced, and I was sort of messing around with relationships and that was all quite turbulent. And then I easily got into, well, that I was really going into panic, and then quickly grabbed those pills again"(man, 58, fully discontinued, describing previous experience)*
Physical problems		Health problems *"I got a hernia when I was halfway through the MBCT course, therefore I wasn't able to finish the training and so I also didn't start tapering the medication" (woman, 62, not discontinued)*
IV. Clinical support		
Professional guidance	Availability and accessibility of clinician support Warranty of being able to restart *"I experienced some tension before starting the tapering. Well I had the guarantee that I could restart whenever necessary (..) you need that reassurance." (man, 68, fully discontinued)*	Negative view of discontinuation by attending clinician *"He [the psychiatrist] said: "I would not do it with your history and family matters". But I wanted to taper (..) and so I did." (woman, 50, partially discontinued)*
Empowerment (self-control)	Sharing ideas about type of support Freedom of choice	Feeling forced

V. Mindfulness practice		
Group context	Peer support *"Never before I had participated in group therapy and to hear from others how they handle tapering and experience the same kind of problems, that gave me some understanding. I liked that. .."(woman, 50, partially discontinued)*	Negative opinion from fellow patients (in MBCT group) who did not taper
Mindfulness skills	Cope with distress *"Then somebody said "why don't you restart medication for a while?" and another said: "go get some antidepressant medication". And then I said, no that is not useful. I know the cause of my problem and I know why I am feeling tense now [financial worries]. Maybe I am a little unhappy now but I am not depressed, I just feel it." (man, 68, fully discontinued)* Relapse prevention *"it [relapse prevention plan] contained elements that made me feel better. Like doing nice things with other people and make sure you keep structure in your day."(woman, 23, fully discontinued)*	

Reporting checklist for qualitative study.

Based on the SRQR guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SRQR reporting guidelines, and cite them as:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. Acad Med. 2014;89(9):1245-1251.

		Reporting Item	Page Number
	#1	Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g. ethnography, grounded theory) or data collection methods (e.g. interview, focus group) is recommended	**1**
	#2	Summary of the key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results and conclusions	**2-3**
Problem formulation	#3	Description and signifcance of the problem / phenomenon studied: review of relevant theory and empirical work; problem statement	**5**
Purpose or research question	#4	Purpose of the study and specific objectives or questions	**5**
Qualitative approach and research paradigm	#5	Qualitative approach (e.g. ethnography, grounded theory, case study, phenomenolgy, narrative research) and	**7**

		guiding theory if appropriate; identifying the research paradigm (e.g. postpositivist, constructivist / interpretivist) is also recommended; rationale. The rationale should briefly discuss the justification for choosing that theory, approach, method or technique rather than other options available; the assumptions and limitations implicit in those choices and how those choices influence study conclusions and transferability. As appropriate the rationale for several items might be discussed together.	
Researcher characteristics and reflexivity	#6	Researchers' characteristics that may influence the research, including personal attributes, qualifications / experience, relationship with participants, assumptions and / or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results and / or transferability	**7**
Context	#7	Setting / site and salient contextual factors; rationale	**6**
Sampling strategy	#8	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g. sampling saturation); rationale	**7**
Ethical issues pertaining to human subjects	#9	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	**6**
Data collection methods	#10	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources / methods, and modification of procedures in response to evolving study findings; rationale	**6-7**
Data collection instruments and technologies	#11	Description of instruments (e.g. interview guides, questionnaires) and devices (e.g. audio recorders) used for data collection; if / how the instruments(s) changed over the course of the study	**7**
Units of study	#12	Number and relevant characteristics of participants, documents, or events included in the study; level of	**12**

		participation (could be reported in results)	
Data processing	#13	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymisation / deidentification of excerpts	**9**
6Data analysis	#14	Process by which inferences, themes, etc. were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale	**9**
Techniques to enhance trustworthiness	#15	Techniques to enhance trustworthiness and credibility of data analysis (e.g. member checking, audit trail, triangulation); rationale	**9, 15,16**
Syntheses and interpretation	#16	Main findings (e.g. interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	**12-16**
Links to empirical data	#17	Evidence (e.g. quotes, field notes, text excerpts, photographs) to substantiate analytic findings	**supplement 1**
Intergration with prior work, implications, transferability and contribution(s) to the field	#18	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application / generalizability; identification of unique contributions(s) to scholarship in a discipline or field	**17**
Limitations	#19	Trustworthiness and limitations of findings	**18**
Conflicts of interest	#20	Potential sources of influence of perceived influence on study conduct and conclusions; how these were managed	**9, 18**
Funding	#21	Sources of funding and other support; role of funders in data collection, interpretation and reporting	**20**

BMJ Open

Discontinuing antidepressant medication after Mindfulness-Based Cognitive Therapy: A mixed-methods study exploring predictors and outcomes of different discontinuation trajectories, and its facilitators and barriers.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039053.R1
Article Type:	Original research
Date Submitted by the Author:	21-Jul-2020
Complete List of Authors:	Huijbers, Marloes; Radboudumc, Psychiatry Wentink, Carolien; Radboudumc, Psychiatry Simons, Esther; Radboudumc, Primary and Community Care Spijker, Jan; Pro Persona Locatie Tarweweg, Expertise Centre for Depression Speckens, Anne; Radboudumc, Psychiatry
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics, Qualitative research
Keywords:	PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, QUALITATIVE RESEARCH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE PAGE

Title:

Discontinuing antidepressant medication after Mindfulness-Based Cognitive Therapy: A mixed-methods study exploring predictors and outcomes of different discontinuation trajectories, and its facilitators and barriers.

Authors:

Marloes J Huijbers [1], Carolien Wentink [1], Esther Simons [2], Jan Spijker [3], Anne EM Speckens [1]*

[1] Department of Psychiatry, Radboud University Medical Centre, Nijmegen, the Netherlands

[2] Department of Primary and Community Care, Radboud University Medical Centre, Nijmegen, the Netherlands

[3] Pro Persona, Expertise Centre for Depression, Nijmegen, the Netherlands

*corresponding author due to maternity leave of Dr. M. Huijbers

Radboud University Medical Centre, department of Psychiatry

Reinier Postlaan 4, 6525 GC Nijmegen

The Netherlands

Tel: 0031-24-3668456

Email: Anne.Speckens@radboudumc.nl

Contact details M. Huijbers:

Tel: 0031-24-3610405

Email: marloes.huijbers@radboudumc.nl

Word count, excluding title page, abstract, references, figures, and tables: 3615.

ABSTRACT

Objectives

This study aimed to explore predictors and outcomes associated with different trajectories of discontinuing antidepressant medication (ADM), in recurrently depressed individuals after participation in Mindfulness-Based Cognitive Therapy (MBCT). Facilitators and barriers of discontinuation were explored qualitatively.

Design:

Mixed-methods study combining quantitative and qualitative data, drawn from a randomized controlled trial.

Setting: Twelve secondary and tertiary psychiatric outpatient clinics in the Netherlands.

Participants: Recurrently depressed individuals (N=226) who had been using ADM for at least six months and in partial or full remission. Regardless of trial condition, we made post-hoc classifications of patients' actual discontinuation trajectories: full discontinuation (n=82), partial discontinuation (n=34) and no discontinuation (n=110) of ADM within six months after baseline. A subset of patients (n=15) and physicians (n=7) were interviewed to examine facilitators and barriers of discontinuation.

Interventions: All participants were offered MBCT, which consisted of eight weekly sessions in a group.

Primary and secondary outcome measures: Demographic and clinical predictors of successful discontinuation within six months, relapse risk within 15 months associated with different discontinuations trajectories, and barriers and facilitators of discontinuation.

Results:

Of the 128 patients assigned to MBCT with discontinuation, only 68 (53%) fully discontinued ADM within 6 months, and 17 (13%) discontinued partially. Predictors of full discontinuation were female sex, being employed and lower levels of depression. Relapse risk was lower after no discontinuation (45%) or partial discontinuation (38%), compared with full discontinuation (66%) ($p = 0.02$). Facilitators and barriers of discontinuation were clustered within five themes: I) pre-existing beliefs about depression, medication and tapering; II) current experience with ADM; III) life circumstances; IV) clinical support; and V) mindfulness.

Conclusions:

Discontinuing antidepressants appears to be difficult, stressing the need to support patients and physicians in this process. MBCT may offer one of these forms of support.

Trial registration: ClinicalTrials.gov: NCT00928980. Post results.

Keywords antidepressants, discontinuation, recurrent depression, mindfulness-based cognitive therapy, barriers and facilitators

ARTICLE SUMMARY

Strengths and limitations of this study

- Rather than using opinions or hypothetical perspectives on tapering, this study used data on the actual discontinuation trajectories that recurrently depressed patients engaged in, and the associated predictors and outcomes.
- The facilitators and barriers reported by patients who attempted to discontinue are in accordance with and support previous findings from the qualitative literature.
- Professionals' perspectives were included to triangulate patients' perspectives on discontinuation of ADM in the qualitative study.
- Reports of relapse/recurrence may have been inflated by withdrawal or post-withdrawal symptoms, which could not be differentiated with the available data.
- Selection bias cannot be ruled out, as participation in the trial might have been influenced by perceptions and preferences regarding both mindfulness and the use of antidepressant medication.

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent mental disorder with a large burden of disease and high risk of recurrence.[1] One of the most commonly used and effective relapse prevention strategies is maintenance antidepressant medication (ADM).[2] Current guidelines recommend patients with MDD to continue medication for at least two years after remission.[3 4] However, patients are often reluctant to use ADM for long periods because of side effects, pregnancy, or interaction with other medication. As discontinuing ADM can be associated with significant withdrawal effects,[5] and increased relapse risk,[6] there has recently been a rise in scientific and clinical interest in this area.[7 8] One of the psychological treatment strategies that have been developed to protect against depressive relapse is Mindfulness Based Cognitive Therapy (MBCT).[9] A recent meta-analysis showed that MBCT is at least as effective in reducing the risk of relapse/recurrence as ADM.[10] As MBCT provides patients support in managing uncomfortable somatic sensations and emotions, it could also help them to deal with possible withdrawal effects and increased emotional reactivity during discontinuation of ADM.[7 11] Two randomized controlled trials (RCTs) in the UK, offering recurrently depressed patients MBCT with additional tapering support, indeed showed successful tapering of ADM in about three quarter of their participants. [12 13] However, studies conducted in the Netherlands showed markedly lower levels of successful tapering, i.e. about half when combined with MBCT[6] or Preventive Cognitive Therapy[14] and only 6% when tapering advise was given without further support.[15]

The aim of this study was to examine possible predictors and outcomes of full, partial and no discontinuation of ADM in recurrently depressed individuals who participated in MBCT in the context of an RCT.[6] In addition, we explored the barriers and facilitators of discontinuation by conducting in-depth qualitative interviews with a subsample of RCT participants and their attending clinicians.

METHODS

Data

Data originated from and RCT comparing MBCT followed by discontinuation or continuation of ADM.[6] For the current paper, groups were created post hoc based on patients' actual discontinuation profiles during the study, i.e. full, partial, or no discontinuation of their ADM. We invited a purposive sample of the participants and their attending clinicians for a semi-structured interview focussing on barriers and facilitators of discontinuation.

Participants

Patients with three or more previous depressive episodes who had been using ADM for 6 months or longer were recruited in 12 secondary and tertiary psychiatric outpatient clinics across the Netherlands between September 2009 and January 2012. For further information on the specific in- and exclusion criteria and process of obtaining informed consent from participants we refer to the publication of the trial itself.[6] The study was approved by the Medical Ethics Committee Arnhem-Nijmegen (nr. 2008/242).

Public and Patient Involvement

At the time of the study, public or patients were unfortunately not yet involved in working with the research funder to prioritise research or offering advice as members of our own project steering group. However, patients and health care professionals in the participating centres were regularly informed about the progress of the study via newsletters. In addition, the qualitative feedback on the barriers and facilitators of MBCT as supportive intervention during discontinuation of ADM has been directly translated into the refinement of an MBCT intervention to support ADM discontinuation, investigated in an RCT conducted between 2015 and 2019 by our group.[16]

Procedure

A detailed description of the study procedures in line with CONSORT guidelines is provided in the RCT report.[6] Eligible patients were randomly assigned to MBCT followed by guided discontinuation of ADM or to MBCT with continuation of ADM. Follow-up quantitative assessments (measures of depression, relapse/recurrence, ADM usage) took place 3, 6, 9, 12, and 15 months after baseline.
For the qualitative part of the study, we adhered as much as possible to the Standards for Reporting Qualitative Research (SRQR).[17] A subset of 15 participants from the MBCT+Discontinuation group were purposively sampled on the basis of age, sex, and discontinuation profile. We kept inviting participants until saturation of the data was established. For the purpose of triangulation, we also included physicians who had guided discontinuation. Interviews were semi-structured, individual and by telephone. Patients and attending physicians were asked the following questions: 1) "What hampered your (the patients') discontinuation process?"; 2) "What facilitated your (the patients') discontinuation process?"; and 3) "What was the role of mindfulness in your (the patients') process of discontinuation?". The interviews were conducted by CW and ES, both female. CW was a psychologist and PhD student on a project investigating ADM discontinuation in primary care. ES was a medical student completing her research internship. Neither of them were acquainted with the participants prior to the interviews.

Interventions

Mindfulness-Based Cognitive Therapy (MBCT)

MBCT was largely based on the protocol by Segal, Williams, and Teasdale[9] and consisted of eight weekly sessions of 2.5 hours and one day of silent practice between the sixth and seventh session. It was delivered in groups of eight to 12 participants and included mindfulness meditation practices, group inquiry, cognitive-behavioural elements, interactive psycho-education, and home practice.

Discontinuation or continuation of ADM

Patients in the discontinuation arm were asked and recommended to gradually withdraw from their ADM over a period of five weeks, starting after the seventh session of MBCT, with specified steps for each of the commonly used types of antidepressants[18] and supervised by their attending physician (mostly psychiatrists) in three to 12 consultations. Patients in the continuation arm were offered a minimum of one consultation. Psychiatrists were instructed to maintain or reinstate an adequate dose of ADM, and recommendations to manage side effects were provided. Full discontinuation was defined as tapering to nil milligrams within six months after baseline. Partial discontinuation was defined as tapering to a lower dose and 'no discontinuation' was defined as maintaining or increasing the initial therapeutic dose of ADM throughout the first six months after baseline.

Outcome measures

Relapse/recurrence rates were compared between the three discontinuation subgroups (full, partial, not). It was assessed using the Structured Clinical Interview for DSM-IV[19] (SCID) 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). Baseline severity of depressive symptoms was measured with the Inventory for Depressive Symptomatology (IDS-C).[20]

Statistical and qualitative analysis

Quantitative analysis

All analyses were performed using SPSS Statistics version 20.0. Probability values lower than 0.05 (two-tailed) were considered significant for all analyses. Possible differences in baseline characteristics between participants who discontinued fully, partially or not at all were examined using independent samples t-tests for continuous and Pearson χ^2 tests for categorical variables.

Relapse/recurrence rates across the entire trial sample, differentiated into three discontinuation profile groups (full, partial, not) were compared with a Pearson χ^2 test and differences in time to relapse/recurrence were analysed using a Cox regression proportional hazards model. Baseline depression severity and number of previous episodes (log transformed) were included as covariates because these factors have been consistently associated with an increased relapse risk.[21] 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.

Qualitative analysis

The qualitative interviews were audio-taped, transcribed verbatim en imported in the scientific qualitative research software program ATLAS.ti (version seven). The constant comparative method was used to develop a theory that was grounded in the data, namely by categorizing, coding, delineating categories and connecting them.[22] Analysis started as soon as the first data were collected and continued with each additional interview. Two researchers (CW, ES) coded the transcripts independently to minimize subjectivity. Subsequently codes were modified and categorized as various facilitators and barriers by the full research team, also consisting of a professor of psychiatry and mindfulness teacher with prior experience with qualitative research (AS) and a psychologist and post-doc researcher (MH). The cycle of comparison and reflection on "old" and "new" themes was repeated several times. Eventually, characteristic quotes were used to illustrate the final themes and subthemes. The original Dutch quotes in this article were translated into English by the authors.

RESULTS

Quantitative results

Flow of ADM discontinuation and intervention adherence

The flow of participants and their ADM use is shown in Figure 1. Of the 249 participants randomized, 128 were allocated to MBCT+Discontinuation and 121 to MBCT+ADM. From 23/249 (9%) patients,

we had insufficient information about ADM use due to early dropout. Consequently, descriptive and statistical analyses were performed on 226 participants.

Of the 82 patients who fully discontinued ADM within six months after baseline, 41 (50%) restarted ADM at some point during the 15-month study period. Based on the SCID interviews, this might have been related to a relapse in 31/41 (76%) of them.

Adherence to MBCT sessions differed significantly between those with a full discontinuation profile M=7.2 ± 1.5 versus the no discontinuation group, M=6.4 ± 2.0 (p = .003). Those who partially discontinued were in between, with an attendance of M=7.0 ± 1.4. The number of medication consultations also differed significantly among the groups, being highest for those with a full discontinuation profile (M=3.0 ± 2.0; range 0-13) versus partial discontinuation (M=2.3 ± 1.4; range 1-6) (p = .03) versus no discontinuation group (M=1.6 ± 1.5; range 0-11) (p < .00). The partial and full discontinuation group did not differ significantly (p = .06).

[Figure 1]

Demographic and clinical characteristics

The demographic and clinical characteristics for the different profile groups are summarized in Table 1. In comparison with those who did not discontinue, females were more likely to fully discontinue than men (76% versus 53%; p = 0.026) and employed participants more likely than those who were unemployed (78% versus 56%; p = 0.002). Those who fully discontinued also had significantly less depressive symptoms at baseline than those who did not (M=10.9 (SD 8.8) vs M=14.4 (SD 10.6), p = 0.018; d = 0.37).

Table 1. Baseline demographic and clinical characteristics of 226 patients with recurrent depression receiving mindfulness-based cognitive therapy who subsequently engaged in full, partial, or no discontinuation of maintenance antidepressant medication (adapted from Huijbers et al, 2016).

	Total N = 226 [a]			
Variable	**Full discontinuation**	**Partial discontinuation**	**No discontinuation**	**Sig.**

	(n = 110)		(n = 34)		(n = 82)		
	N	%	N	%	N	%	*p*
Female	62	76	18	53	71	64	**0.048**
Educational level							0.421
-Low	7	9	3	9	6	6	
-Middle	24	29	10	29	31	28	
-High	49	60	21	62	64	58	
-Missing	2	2	0	0	9	8	
Marital status							0.560
-Single	19	23	6	18	27	25	
-Married/cohabiting	46	56	22	65	60	55	
-Divorced/widowed	15	18	6	18	16	15	
-Missing	2	2	0	0	7	6	
Employed (n=225)	63	78	22	65	62	56	**0.009**
Remission							0.069
-Full, IDS-C ≤ 11	51	62	17	50	50	45	
-Partial, IDS-C > 11	31	38	17	50	60	55	
Type of mADM							0.669
-SSRI	64	78	23	68	21	19	
-TCA	13	16	7	21	21	19	
-Other [b]	5	6	4	12	6	6	
Previous CBT treatment	45	55	21	62	68	62	0.595
Suicide attempt (lifetime)	18	22	12	15	21	49	0.429
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	50.0	11.1	52.0	9.8	51.0	10.3	0.507
Baseline depression (IDS-C)	10.9	8.8	12.7	11.2	14.4	10.6	0.059
Nr. previous episodes	5.6	4.9	7.4	8.0	5.7	3.9	0.167
Age at MDD onset (n=219)	27	11.9	25	10.8	25.0	12.3	0.388

Legend: IDS-C, Inventory of Depressive Symptomatology – Clinician rated; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; CBT, cognitive-behavioural therapy; MDD, major depressive disorder.

[a] Excluding 23 of the original 249 trial participants due to missing data regarding discontinuation.

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

Relapse and recurrence

Rates of relapse were 66% for full discontinuation, 38% for partial discontinuation and 45% for no discontinuation. As illustrated in Figure 2, Cox regression analysis with baseline level of depression and number of previous episodes (log transformed) as covariates showed that there were significant

differences in terms of risk of relapse across the three groups (p = 0.02). Compared with the full discontinuation group, those who did not discontinue had a lower risk of relapse (hazard ratio = 0.67; 95% CI = 0.45 – 0.99; p = 0.04). The lowest risk of relapse was seen for those who partially discontinued, compared with full discontinuation (hazard ratio = 0.47; 95% CI = 0.26 – 0.87; p = 0.02). There was no significant difference in relapse risk between partial and no discontinuation (p = 0.27).

[Figure 2]

Qualitative results

The interviewed patients consisted of eight women and nine men, with a mean IDS-score at baseline of 11 ± 7.8. See Table 2 for their characteristics. Nine patients discontinued their ADM fully, three partially and three did not discontinue their ADM.

Table 2. Patients' characteristics for the subset of participants in the qualitative study.

Patient	Sex	Age range	IDS at baseline	Discontinuation ≤6 months	Relapse ≤15 months
P1	male	30-39	9	Partially	No
P2	male	40-49	15	Not	No
P3	female	30-39	10	Fully	Yes
P4	female	20-29	10	Fully	Yes
P5	male	60-69	0	Fully	Yes
P6	female	50-59	13	Partially	Yes
P7	male	70-79	10	Fully	No
P8	female	50-59	17	Partially	Yes
P9	male	50-59	3	Not	Yes
P10	male	60-69	30	Fully	Yes
P11	female	60-69	20	Not	Yes
P12	female	50-59	7	Fully	Yes
P13	male	50-59	14	Fully	No
P14	female	30-39	14	Fully	Yes
P15	female	60-69	0	Fully	No

Five themes emerged from the patient interviews: I) patients' pre-existing beliefs about depression, medication and tapering; II) current experience with antidepressants; III) psychosocial conditions and physical problems; IV) clinical support and V) participating in MBCT. The most significant subthemes are described in more detail below. See online supplement 1 for an overview of themes, subthemes and illustrating quotes.

I. Pre-existing beliefs about depression, medication and tapering

Facilitators

Being aware that others are also subject to periods of low mood and feeling downhearted occasionally seemed to facilitate the process of discontinuation. This was accompanied by the realization that medication is not always needed to suppress those feelings. Although most respondents had regarded their medication as helpful during their depression, some patients considered taking pills for long periods of time as unhealthy and even 'harmful'. Respondents also talked about their wish to manage without pills.

Barriers

Several respondents mentioned that they were (told to be) missing a specific substance in their brain and therefore needed ADM. They considered their condition as chronic and medication as necessary. Not surprisingly, these people were reluctant to (fully) taper their medication. Another central theme was the fear of relapse in depression. Several patients expressed concern that this would happen. On a related note, many participants had tried to come off medication in the past and experienced difficulties, i.e. withdrawal symptoms.

II. Current experience with antidepressants

Facilitators

There were patients describing uncertainty about the benefits of taking their medication. In addition, the occurrence of unwanted or 'side' effects emerged as a theme. In addition, being able to adopt a personalized tapering schedule facilitated the discontinuation process. Such a personalized schedule typically contained adaptations with regard to the duration and magnitude of the dose reductions, or were much more flexible so that tapering could be guided by their own mental health state.

Barriers

Some participants for whom ADM were still beneficial in managing depressive symptoms did not start discontinuation. Withdrawal effects appeared one of the major reasons to interrupt discontinuation, restart or increase the dose of medication. For many patients the tapering speed according to the RCT guideline was considered too fast. One patient said, for example: "*I was using Citalopram and I believe I had to taper within 2 weeks, but I was suffering quite a lot from withdrawal symptoms, so therefore, after consultation, tapered somewhat more slowly.*"

III. Life circumstances

Facilitators

In a relatively quiet period, people appeared more likely to start and proceed with tapering.

Barriers

If there were stressful circumstances (for example, work-related problems), a lack of support from family or friends, or health problems, people seemed more reluctant to start or continue the tapering process.

IV Clinical support

Facilitators

Availability and accessibility of professional guidance was an important facilitator, both before and during the tapering process. Patients mentioned the importance of bringing in their own ideas of how clinical support would ideally look like, and having the freedom to choose for themselves what they felt was best. Reassurance about being able to restart medication in case of deterioration was also described as helpful.

Barriers

In some cases the attending clinician would advise against discontinuation, which was mentioned as a barrier: "*He [the psychiatrist] said: "I would not do it with your history and family matters". But I wanted to taper (..) and so I did."*. Another barrier that emerged from the interviews was the impression that, possibly related to the context of the RCT, tapering was mandatory.

V. Mindfulness practice

Facilitators

Participants mentioned peer support in MBCT as a facilitating factor. Witnessing how other people deal with similar problems and sharing fears and insecurities about tapering were regarded as helpful and reassuring. In addition, mindfulness itself had been a source of support during tapering, for example being able to distinguish feelings of stress from a depressive relapse and recognizing that these were triggered by difficult psychosocial circumstances, which did not necessarily require to restart medication. Mindfulness practice also provided an alternative method to prevent depressive relapse, by recognizing periods of increased vulnerability and using other approaches rather than increasing the dose of ADM (e.g. daily walks in nature, seeing friends and reducing workload).

Barriers

The MBCT group context could also negatively impact the process. MBCT groups included participants from both arms of the RCT, including those who were asked to continue ADM after MBCT. It was mentioned that sometimes fellow group members, who continued their medication, advised against discontinuation.

Facilitators and barriers as reported by attending clinicians

Fourteen patients gave permission to interview their attending physician, of whom seven were willing and able to participate. See Table 3 for their characteristics.

Table 3. Professionals' characteristics.

Professional	Sex	Age range	Function	Institute
PF1	female	50-59	psychiatrist	university medical center
PF2	female	30-39	psychiatrist in training	university medical center
PF3	female	40-49	psychiatrist	mental health institute
PF4	female	40-49	physician	university medical center
PF5	male	60-69	psychiatrist	private practice
PF6	female	50-59	psychiatrist	university medical center
PF7	male	40-49	psychiatrist	mental health institute

Professionals' perspectives generally showed a large overlap with the views expressed by participants. For example, the benefits of tapering slowly and with a personalized tapering scheme clearly emerged from these interviews. In terms of barriers, the pivotal roles of negative experiences with tapering in the past, worrying about symptoms and possible relapse, and stressful circumstances were mentioned.

Some different themes emerged from these interviews as well. Clinicians reported feeling reluctant to discontinue ADM because of their own worries about patients having a relapse, especially in case of a long psychiatric history or comorbidity. They spoke more specifically about ADM characteristics

(half-life time) and switching to a different type of ADM before fully discontinuing as a possible facilitator. They also mentioned the possible use of other psychological interventions to help patients cope with emerging symptoms. Regarding barriers, clinicians were particularly concerned about nocebo effects when discussing potential withdrawal effects, suggesting to provide some information but avoiding being very specific about it.

DISCUSSION

Principal findings

The current paper provides quantitative post-hoc data from an RCT, describing the flow, characteristics and outcomes of patients with recurrent depression who discontinued ADM fully, partially or not at all. Quantitative data were complemented by qualitative data on the barriers and facilitators of ADM withdrawal. In the original MBCT+discontinuation treatment arm, only 53% of the participants were able to fully discontinue within six months from baseline, 13% discontinued partially and 25% of the participants decided to continue their medication as it was despite the randomization. Notably, discontinuation also occurred in patients asked to continue their medication: 12% discontinued fully and 14% partially. These non-compliance rates and apparent difficulties with discontinuation are in line with previously published studies on (preventive) cognitive therapy for recurrently depressed patients[23] and anxiety disorders.[24]

Full discontinuation occurred more frequently in women, and in those who were employed. Indeed, the qualitative data point to psychosocial stressors as possible barriers to discontinuation, and problems with finding or holding on to a suitable job might be one of them. In addition, tapering appeared more feasible for those with lower levels of baseline depression. In contrast, the qualitative data suggest that if ADM are considered an effective treatment to reduce or manage depressive symptoms, patients are *less* likely to taper, and vice versa. Possibly, these beliefs may vary over time and across circumstances. For example, a patient who considers tapering because ADM has not been very effective, but would nevertheless postpone this because of a current episode of depression.

Even in those participants who discontinued completely in the current study, more than half restarted medication within the next nine months, possibly related to relapse or recurrence of depression. Relapse rates were indeed substantially higher for fully discontinued patients than for partially and not discontinued. These differences seem clinically relevant, and may even advocate partial rather than full discontinuation. While linear tapering regimes are commonplace, the most challenging part of the withdrawal process may occur at the lowest doses. As this might have to do with hyperbolic dose-response relationships between drugs such as selective serotonin reuptake inhibitors and their receptor,[25] it has been suggested that "stop slow if you go low" regimes may help to minimize withdrawal symptoms.[26] Although the use of "tapering strips" can be a suitable way to taper gradually,[27] for many types of ADM these are not yet available.

In line with a recent systematic review,[28] worry and fear of relapse emerged as clear barriers to discontinuation in the qualitative interviews. These fears appear to exist not only for patients, but also for attending physicians. Some professionals reported being anxious about responsibility for deterioration and sometimes feeling unable to help, which has also been reported in previous studies.[29] For both patients and professionals, accessibility and availability of support during tapering is important.

Strengths and weaknesses

A major strength of the current study is that we combined quantitative and qualitative data to investigate what makes it more difficult or easy to discontinue ADM. Rather than using opinions or hypothetical perspectives on tapering, we report data on the actual tapering process in an RCT, including clinical outcomes, in which full, partial and no discontinuation were defined before the study started [18]. In addition, we looked at professionals' perspectives to triangulate patients' perspectives on discontinuation of ADM in the qualitative study.

One of the limitations of the current study is that reports of relapse/recurrence may have been inflated by withdrawal or post-withdrawal symptoms. Chouinard and Chouinard have developed criteria permitting identification of three types of withdrawal problems associated with SSRIs: new

withdrawal symptoms, rebound and persistent post withdrawal disorder, which can be differentiated from relapse and recurrence.[30] As withdrawal symptoms were not included as an outcome measure, we could unfortunately not differentiate this in our RCT.

Another limitation is that due to the set-up of the current trial, there is no control group of patients withdrawing from antidepressant medication who do not receive MBCT. Consequently, predictors of discontinuation of antidepressants with MCBT might be predictors of the take up of MCBT rather than discontinuation of ADM. The same issue might may apply to the discontinuation outcomes. These issues might be conflated by the differences found in attendance at MCBT sessions. Although we did collect some baseline demographic and clinical characteristics that might influence discontinuation, this obviously does not include all the factors that a prescribing clinician would consider before recommending discontinuation. For instance there are no measures of patient's subjective readiness to discontinue, mental and physical comorbidity or other baseline medication which might lead to adverse effects on the patient. This is a limitation of predictors of discontinuation and may confound those factors that have been identified as well as outcome. These factors may also be important to understand why there might be differences in outcome with MCBT on ADM discontinuation across studies.

In addition, we cannot rule out selection bias, as participation in the trial might have been influenced by perceptions of both mindfulness and ADM. Participants in the qualitative part of the study may be more positive about MBCT than those who dropped out of the intervention. In addition, the number of professionals contributing to the qualitative interview data was rather small.

Clinical recommendations

First and foremost, our findings clearly point to the necessity of up-to-date, accessible and professional guidance for those who wish to come off their ADM. A recently published shared decision making tool[31] might assist patients and their clinicians in their consultations. Secondly, a personalized tapering approach seems essential to enable successful tapering. With accumulating evidence suggesting that slow tapering is associated with better outcomes,[32] it is important to slow down the pace of tapering on

the basis of patients' preferences and needs. Finally, results from the current study point to the possible clinical relevance of tapering to low doses of ADM rather than complete withdrawal. This might prevent withdrawal symptoms, whether neurochemical or psychological, empower patients by letting them choose their optimal dose, and reduce side effects and health care costs.

Research implications

So far, it remains unclear whether the increased risk of relapse and withdrawal symptoms are a direct effect of neurobiological changes, or an indirect effect driven by psychological mechanisms such as fear of relapse, negative expectations based on previous failed tapering attempts, or nocebo effects caused by information about withdrawal symptoms. To disentangle these effects at a more fundamental level, a double-blind withdrawal study with active versus placebo pills should be conducted.

In addition, future research might focus on the effectiveness of protocolized tapering support interventions and existing psychological interventions that might be helpful to manage withdrawal symptoms and depression. Besides MBCT, Preventive Cognitive Therapy might be a valuable option.[14] Future studies should include homogeneous groups of patients who are all in the same phase of discontinuation. We are currently conducting an RCT in primary care inviting long-term ADM users who have made a shared decision to discontinue, are supported by mental health assistants or their GP in devising and monitoring their tapering process, and are either offered additional MBCT or not.[16]

Funding statement

The RCT from which data were drawn was funded by ZonMW, the Netherlands Organization for Health Research and Development (Grant no. 170992903 awarded to Prof. A.E.M. Speckens). No additional funding was requested for the current mixed-methods study. The funder had no role in the writing of the manuscript or the decision to submit it for publication.

Data sharing

We aim to make our data available for other researchers as much as possible, albeit with a restricted access policy. As data are currently not yet filed in a public repository, researchers interested in re-using our data are invited to contact the authors.

Competing interests

MH and AS report grants from ZonMW Doelmatigheid, during the conduct of the study; CW, ES and JS have nothing to disclose.

Author contributions

MH and AS led the RCT from which the quantitative data were drawn. For the current study, MH, CW, JS and AS formulated the study design. MH and CW collected data. ES assisted with data collection. MH and CW contributed to data analysis and data interpretation. MH wrote the manuscript and prepared the figures and tables. CW, ES, JS and AS edited the manuscript.

Acknowledgements

The authors would like to acknowledge all participants who have contributed to this work, as well as all health care professionals who have participated in the trial and those who contributed to the qualitative interviews.

REFERENCES

1. Richards D. Prevalence and clinical course of depression: a review. *Clinical psychology review* 2011;31(7):1117-25. doi: 10.1016/j.cpr.2011.07.004 [published Online First: 2011/08/09]
2. Gueorguieva R, Chekroud AM, Krystal JH. Trajectories of relapse in randomised, placebo-controlled trials of treatment discontinuation in major depressive disorder: an individual patient-level data meta-analysis. *The lancet Psychiatry* 2017;4(3):230-37. doi: 10.1016/s2215-0366(17)30038-x [published Online First: 2017/02/13]
3. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (3rd ed.): APA, 2010.
4. National Institute for Health and Care Excellence. Depression in adults: recognition and management. CG90. London: NICE, 2009.
5. Davies J, Read J. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? *Addictive behaviors* 2019;97:111-21.
6. Huijbers MJ, Spinhoven P, Spijker J, et al. Discontinuation of antidepressant medication after mindfulness-based cognitive therapy for recurrent depression: randomised controlled non-inferiority trial. *British Journal of Psychiatry* 2016;208(4):366-73. doi: 10.1192/bjp.bp.115.168971
7. Maund E, Stuart B, Moore M, et al. Managing Antidepressant Discontinuation: A Systematic Review. *Annals of family medicine* 2019;17(1):52-60. doi: 10.1370/afm.2336 [published Online First: 2019/01/24]
8. Bowers HM, Kendrick T, Glowacka M, et al. Supporting antidepressant discontinuation: the development and optimisation of a digital intervention for patients in UK primary care using a theory, evidence and person-based approach. *BMJ Open* 2020;10(3):e032312. doi: 10.1136/bmjopen-2019-032312 [published Online First: 2020/03/11]
9. Segal, Williams JMG, Teasdale JD. Mindfulness-Based Cognitive Therapy for Depression, 2nd edn.: Guilford Press 2012.
10. Kuyken W, Warren FC, Taylor RS, et al. Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse: An Individual Patient Data Meta-analysis From Randomized Trials. *JAMA Psychiatry* 2016;73(6):565-74. doi: 10.1001/jamapsychiatry.2016.0076 [published Online First: 2016/04/28]
11. Tickell A, Byng R, Crane C, et al. Recovery from recurrent depression with mindfulness-based cognitive therapy and antidepressants: a qualitative study with illustrative case studies. *BMJ Open* 2020;10(2):e033892. doi: 10.1136/bmjopen-2019-033892 [published Online First: 2020/02/23]
12. Kuyken W, Byford S, Taylor RS, et al. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. *J Consult Clin Psychol* 2008;76(6):966-78. doi: 10.1037/a0013786 [published Online First: 2008/12/03]
13. Kuyken W, Hayes R, Barrett B, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. *Lancet (London, England)* 2015;386(9988):63-73. doi: 10.1016/s0140-6736(14)62222-4 [published Online First: 2015/04/25]
14. Bockting CL, Klein NS, Elgersma HJ, et al. Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. *The Lancet Psychiatry* 2018;5(5):401-10.
15. Eveleigh R, Muskens E, Lucassen P, et al. Withdrawal of unnecessary antidepressant medication: a randomised controlled trial in primary care. *BJGP Open* 2018;1(4):bjgpopen17X101265.
16. Wentink C, Huijbers MJ, Lucassen P, et al. Discontinuation of antidepressant medication in primary care supported by monitoring plus mindfulness-based cognitive therapy versus

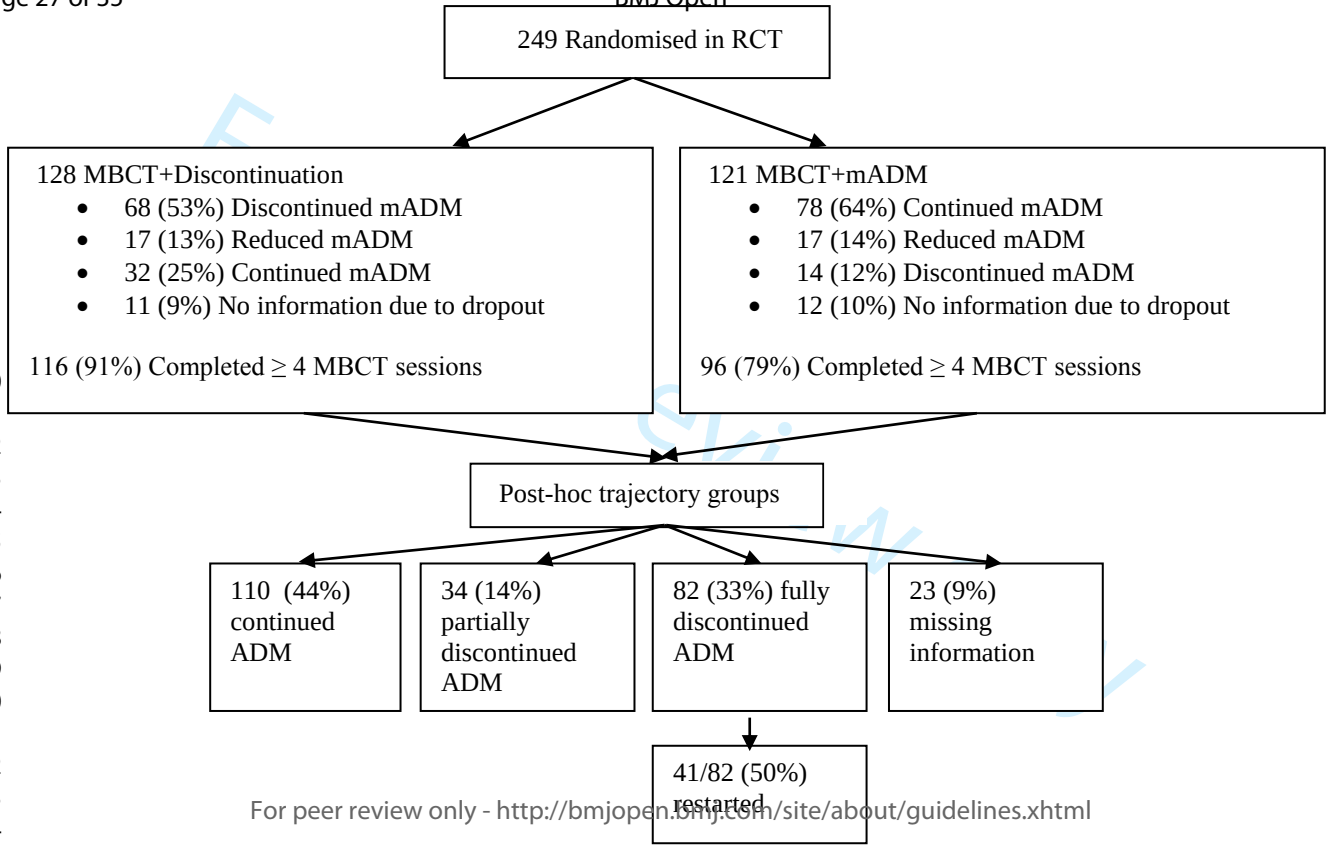
monitoring alone: design and protocol of a cluster randomized controlled trial. *BMC family practice* 2019;20(1):105.
17. O'Brien BC, Harris IB, Beckman TJ, et al. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med* 2014;89(9):1245-51. doi: 10.1097/acm.0000000000000388 [published Online First: 2014/07/01]
18. Huijbers MJ, Spijker J, Donders AR, et al. Preventing relapse in recurrent depression using mindfulness-based cognitive therapy, antidepressant medication or the combination: trial design and protocol of the MOMENT study. *BMC Psychiatry* 2012;12(1):125. doi: 10.1186/1471-244x-12-125 [published Online First: 2012/08/29]
19. First MB, Gibbon M, Spitzer RL, et al. User's guide for the structured clinical interview for DSM-IV axis I Disorders—Research version. *New York: Biometrics Research Department, New York State Psychiatric Institute* 1996
20. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): Psychometric properties. *Psychol Med* 1996;26(3):477-86.
21. Hardeveld F, Spijker J, De Graaf R, et al. Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatr Scand* 2010;122(3):184-91. doi: 10.1111/j.1600-0447.2009.01519.x [published Online First: 2009/12/17]
22. Boeije H. A purposeful approach to the constant comparative method in the analysis of qualitative interviews. *Quality and quantity* 2002;36(4):391-409.
23. Bockting CLH, Klein NS, Elgersma HJ, et al. Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. *The lancet Psychiatry* 2018;5(5):401-10. doi: 10.1016/s2215-0366(18)30100-7 [published Online First: 2018/04/08]
24. Scholten WD, Batelaan NM, van Oppen P, et al. The Efficacy of a Group CBT Relapse Prevention Program for Remitted Anxiety Disorder Patients Who Discontinue Antidepressant Medication: A Randomized Controlled Trial. *Psychotherapy and psychosomatics* 2018;87(4):240-42. doi: 10.1159/000489498 [published Online First: 2018/06/04]
25. Meyer JH, Wilson AA, Sagrati S, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. *Am J Psychiatry* 2004;161(5):826-35. doi: 10.1176/appi.ajp.161.5.826 [published Online First: 2004/05/04]
26. Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. *The lancet Psychiatry* 2019;6(6):538-46. doi: 10.1016/s2215-0366(19)30032-x [published Online First: 2019/03/10]
27. Groot PC, van Os J. Antidepressant tapering strips to help people come off medication more safely. *Psychosis* 2018;10(2):142-45. doi: 10.1080/17522439.2018.1469163
28. Maund E, Dewar-Haggart R, Williams S, et al. Barriers and facilitators to discontinuing antidepressant use: A systematic review and thematic synthesis. *Journal of affective disorders* 2019;245:38-62. doi: 10.1016/j.jad.2018.10.107 [published Online First: 2018/10/27]
29. Bowers HM, Williams SJ, Geraghty AWA, et al. Helping people discontinue long-term antidepressants: views of health professionals in UK primary care. *BMJ Open* 2019;9(7):e027837. doi: 10.1136/bmjopen-2018-027837 [published Online First: 2019/07/07]
30. Chouinard G, Chouinard VA. New Classification of Selective Serotonin Reuptake Inhibitor Withdrawal. *Psychotherapy and psychosomatics* 2015;84(2):63-71. doi: 10.1159/000371865 [published Online First: 2015/02/28]
31. Wentink C, Huijbers MJ, Lucassen PLBJ, et al. Enhancing shared decision making about discontinuation of antidepressant medication: a concept-mapping study in primary and secondary mental health care. *British Journal of General Practice* 2019 doi: 10.3399/bjgp19X706001

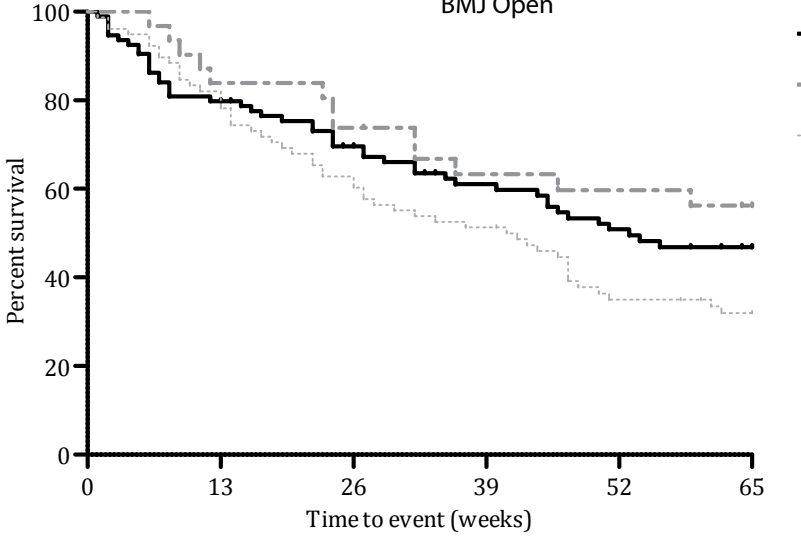
32. Baldessarini RJ, Tondo L, Ghiani C, et al. Illness risk following rapid versus gradual discontinuation of antidepressants. *The American journal of psychiatry* 2010;167(8):934-41. doi: 10.1176/appi.ajp.2010.09060880 [published Online First: 2010/05/19]

Figure captions

Figure 1. Flow chart of participants, their adherence to mindfulness-based cognitive therapy (MBCT) and their use of antidepressant medication (ADM).

Figure 2. Survival curves over 15-month follow up for risk of relapse in recurrently depressed patients with different profiles of discontinuing antidepressant medication: fully (n=82), partially (n=34) or not (n=110).





Number at risk

No discont.	110	74	59	48	38	0
Partial discont.	34	25	22	18	17	0
Full discont.	82	61	47	40	25	0

Online supplement 1. Facilitators and barriers in the discontinuation of antidepressant medication as experienced by patients with recurrent depression who had participated in an MBCT course. Most subthemes are illustrated with quotes in italic.

THEMES	FACILITATORS TO DISCONTINUATION	BARRIERS TO DISCONTINUATION
I Pre-existing beliefs		
About depression	Common humanity *"I noticed that I, well, that I am not always feeling that cheerful. And I have accepted myself as such by now, this is who I am" (woman, 50-59, partially discontinued)*	Missing substance in the brain *"So I thought, well there is just something wrong in your brain and you will have to learn to live with that" (man, 60-69, fully discontinued, describing a previous experience)*
About medication	ADM as harmful *"Yes actually I wanted to get rid of that junk. I call it junk now, but of course it is a beautiful invention, glad that it exists, but I still think .. well, if I can do it without pills." (man, 50-59, not discontinued)* Dependency as weakness *"I want to be able to do it myself. It also felt somewhat like a weakness, that you would need a pill to feel reasonably well" (woman,20-29, fully discontinued)*	Accepting long-term use *"At a certain moment I thought well, life without medication, well for some people this could be an option I guess, but not for me." (man, 30-39, partially discontinued)*
About tapering	Open mind *"I actually noticed very soon that I benefited from the exercises. Then I thought, consider I start withdrawing and I then have a relapse. (…) But on the other hand, I already felt so much better that I thought: well, who knows? I just see what will happen." (man, 60-69, fully discontinued)*	Fear of relapse in depression *"That you relapse into a more severe depression than before (..) And I have had such an experience and did not want to go through that again." (woman, 50-59, partially discontinued)* Previous negative experiences with withdrawal effects during tapering

		"With short… that you are just not ready to quickly…, my body could just not take it. I had all kinds of negative effects from withdrawing, all kinds of symptoms I got." (woman, 50-59, partially discontinued)
II. Current experience with antidepressants		
Effectiveness	ADM does not help (anymore) *"… the idea that those things are not helping me anyway. I thought well, I am taking poison, and it doesn't really help." (man, 60-69, fully discontinued)*	ADM (still) works for me *"… if you are down and out again, then you actually already know it calls for another pill again, so to speak." (man, 50-59, not discontinued)*
Side effects	Side effects when using ADM *"Because I feel that my memory has gotten really worse. And when I was still fully on medication I noticed that my hands were just trembling a lot, and well.. I regarded that as a very bad sign (..) so I thought, I have to get rid of that." (woman, 50-59, partially discontinued)*	N/A
Withdrawal effects	N/A	Withdrawal effects *"I was using Citalopram and I believe I had to taper within 2 weeks, but I was suffering quite a lot from withdrawal symptoms, so therefore, after consultation, tapered somewhat more slowly." (woman, 20-29, fully discontinued)*
Tapering schedule	Individual, step by step *"And then it was advised to taper within 6 months, I discussed that with my doctor and he was not very keen on that and I thought I do not want to fall back again as I had done before. So for sure I am not going to taper as fast as the six months they suggested." (woman, 50-59, partially discontinued)*	Too fast and/or steps too big *"… so I have got something of a bit more tailoring to the person rather than just following the rules from the books" (man, 40-49, not discontinued)*

III. Life circumstances		
Psychosocial conditions	Relatively quiet period *"Just a quiet period so I thought I could put it to the test." (man, 60-69, fully discontinued)*	Social stressors *"I had just divorced, and I was sort of messing around with relationships and that was all quite turbulent. And then I easily got into, well, that I was really going into panic, and then quickly grabbed those pills again"(man, 50-59, fully discontinued, describing previous experience)*
Physical problems	N/A	Health problems *"I got a hernia when I was halfway through the MBCT course, therefore I wasn't able to finish the training and so I also didn't start tapering the medication" (woman, 60-69, not discontinued)*
IV. Clinical support		
Professional guidance	Availability and accessibility of clinician support *"And when there are signs that it doesn't go well, and there were, I just got a lot of support to really, yes, to keep it under control. And to just really stay with it." (woman, 20-29, completed)*	Negative view of discontinuation by attending clinician *"He [the psychiatrist] said: "I would not do it with your history and family matters". But I wanted to taper (..) and so I did." (woman, 50-59, partially discontinued)*
Empowerment (self-control)	Sharing ideas about type of support *"Time and listening to what people try to say. And not just*	Feeling forced *"The pressure to participate in the part of withdrawing medication, I*

	suddenly stopping everything, like it's always like this. Taking it seriously. (…) And I got offered a different kind of therapy." (woman, 50-59, partially discontinued) Freedom of choice *"I did feel a little tense before we started withdrawing. And, well, at a given moment you did have the guarantee that you if it really went wrong, you could always get back." (man, 60-69, fully discontinued)*	*actually found too high." (woman, 60-69, not discontinued)*
V. Mindfulness practice		
Group context	Peer support *"Never before I had participated in group therapy and to hear from others how they handle tapering and experience the same kind of problems, that gave me some understanding. I liked that. .." (woman, 50-59, partially discontinued)*	Negative opinion from fellow patients (in MBCT group) who did not taper *"So others were very fearful about it, those who were not in the group who were allowed or made to discontinue. They said, I would be careful with this, and so on. Yes, and I had the same idea." (man, 60-69, fully discontinued).*
Mindfulness skills	Cope with distress *"Then somebody said "why don't you restart medication for a while?" and another said: "go get some antidepressant medication". And then I said, no that is not useful. I know the cause of my problem and I know why I am feeling tense now [financial worries]. Maybe I am a little unhappy now but I am not depressed, I just feel it." (man, 60-69, fully discontinued)* Relapse prevention	

"it [relapse prevention plan] contained elements that made me feel better. Like doing nice things with other people and make sure you keep structure in your day."(woman, 20-29, fully discontinued)

Reporting checklist for qualitative study.

Based on the SRQR guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SRQR reporting guidelines, and cite them as:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. Acad Med. 2014;89(9):1245-1251.

		Reporting Item	Page Number
	#1	Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g. ethnography, grounded theory) or data collection methods (e.g. interview, focus group) is recommended	**1**
	#2	Summary of the key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results and conclusions	**2-3**
Problem formulation	#3	Description and signifcance of the problem / phenomenon studied: review of relevant theory and empirical work; problem statement	**5**
Purpose or research question	#4	Purpose of the study and specific objectives or questions	**5**
Qualitative approach and research paradigm	#5	Qualitative approach (e.g. ethnography, grounded theory, case study, phenomenolgy, narrative research) and	**7**

		guiding theory if appropriate; identifying the research paradigm (e.g. postpositivist, constructivist / interpretivist) is also recommended; rationale. The rationale should briefly discuss the justification for choosing that theory, approach, method or technique rather than other options available; the assumptions and limitations implicit in those choices and how those choices influence study conclusions and transferability. As appropriate the rationale for several items might be discussed together.	
Researcher characteristics and reflexivity	#6	Researchers' characteristics that may influence the research, including personal attributes, qualifications / experience, relationship with participants, assumptions and / or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results and / or transferability	**7**
Context	#7	Setting / site and salient contextual factors; rationale	**6**
Sampling strategy	#8	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g. sampling saturation); rationale	**7**
Ethical issues pertaining to human subjects	#9	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	**6**
Data collection methods	#10	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources / methods, and modification of procedures in response to evolving study findings; rationale	**6-7**
Data collection instruments and technologies	#11	Description of instruments (e.g. interview guides, questionnaires) and devices (e.g. audio recorders) used for data collection; if / how the instruments(s) changed over the course of the study	**7**
Units of study	#12	Number and relevant characteristics of participants, documents, or events included in the study; level of	**12**

		participation (could be reported in results)	
Data processing	#13	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymisation / deidentification of excerpts	**9**
6Data analysis	#14	Process by which inferences, themes, etc. were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale	**9**
Techniques to enhance trustworthiness	#15	Techniques to enhance trustworthiness and credibility of data analysis (e.g. member checking, audit trail, triangulation); rationale	**9, 15,16**
Syntheses and interpretation	#16	Main findings (e.g. interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	**12-16**
Links to empirical data	#17	Evidence (e.g. quotes, field notes, text excerpts, photographs) to substantiate analytic findings	**supplement 1**
Intergration with prior work, implications, transferability and contribution(s) to the field	#18	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application / generalizability; identification of unique contributions(s) to scholarship in a discipline or field	**17**
Limitations	#19	Trustworthiness and limitations of findings	**18**
Conflicts of interest	#20	Potential sources of influence of perceived influence on study conduct and conclusions; how these were managed	**9, 18**
Funding	#21	Sources of funding and other support; role of funders in data collection, interpretation and reporting	**20**

BMJ Open

Discontinuing antidepressant medication after Mindfulness-Based Cognitive Therapy: A mixed-methods study exploring predictors and outcomes of different discontinuation trajectories, and its facilitators and barriers.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039053.R2
Article Type:	Original research
Date Submitted by the Author:	15-Sep-2020
Complete List of Authors:	Huijbers, Marloes; Radboudumc, Psychiatry Wentink, Carolien; Radboudumc, Psychiatry Simons, Esther; Radboudumc, Primary and Community Care Spijker, Jan; Pro Persona Locatie Tarweweg, Expertise Centre for Depression Speckens, Anne; Radboudumc, Psychiatry
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics, Qualitative research
Keywords:	PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, QUALITATIVE RESEARCH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE PAGE

Title:

Discontinuing antidepressant medication after Mindfulness-Based Cognitive Therapy: A mixed-methods study exploring predictors and outcomes of different discontinuation trajectories, and its facilitators and barriers.

Authors:

Marloes J Huijbers [1*], Carolien Wentink [1], Esther Simons [2], Jan Spijker [3], Anne EM Speckens [1]

[1] Department of Psychiatry, Radboud University Medical Centre, Nijmegen, the Netherlands

[2] Department of Primary and Community Care, Radboud University Medical Centre, Nijmegen, the Netherlands

[3] Pro Persona, Expertise Centre for Depression, Nijmegen, the Netherlands

*corresponding author

Radboud University Medical Centre, department of Psychiatry

Reinier Postlaan 4, 6525 GC Nijmegen

The Netherlands

Tel: 0031-24-3610405

Email: marloes.huijbers@radboudumc.nl

Word count, excluding title page, abstract, references, figures, and tables: 4387

ABSTRACT

Objectives

This study aimed to explore predictors and outcomes associated with different trajectories of discontinuing antidepressant medication (ADM), in recurrently depressed individuals after participation in Mindfulness-Based Cognitive Therapy (MBCT). Facilitators and barriers of discontinuation were explored qualitatively.

Design:

Mixed-methods study combining quantitative and qualitative data, drawn from a randomized controlled trial.

Setting: Twelve secondary and tertiary psychiatric outpatient clinics in the Netherlands.

Participants: Recurrently depressed individuals (N=226) who had been using ADM for at least six months and in partial or full remission. Regardless of trial condition, we made post-hoc classifications of patients' actual discontinuation trajectories: full discontinuation (n=82), partial discontinuation (n=34) and no discontinuation (n=110) of ADM within six months after baseline. A subset of patients (n=15) and physicians (n=7) were interviewed to examine facilitators and barriers of discontinuation.

Interventions: All participants were offered MBCT, which consisted of eight weekly sessions in a group.

Primary and secondary outcome measures: Demographic and clinical predictors of successful discontinuation within six months, relapse risk within 15 months associated with different discontinuations trajectories, and barriers and facilitators of discontinuation.

Results:

Of the 128 patients assigned to MBCT with discontinuation, only 68 (53%) fully discontinued ADM within 6 months, and 17 (13%) discontinued partially. Predictors of full discontinuation were female sex, being employed and lower levels of depression. Relapse risk was lower after no discontinuation (45%) or partial discontinuation (38%), compared with full discontinuation (66%) ($p = 0.02$). Facilitators and barriers of discontinuation were clustered within five themes: I) pre-existing beliefs about depression, medication and tapering; II) current experience with ADM; III) life circumstances; IV) clinical support; and V) mindfulness.

Conclusions:

Discontinuing antidepressants appears to be difficult, stressing the need to support patients and physicians in this process. MBCT may offer one of these forms of support.

Trial registration: ClinicalTrials.gov: NCT00928980. Post results.

Keywords antidepressants, discontinuation, recurrent depression, mindfulness-based cognitive therapy, barriers and facilitators

ARTICLE SUMMARY

Strengths and limitations of this study

- Rather than using opinions or hypothetical perspectives on tapering, this study used data on the actual discontinuation trajectories that recurrently depressed patients engaged in, and the associated predictors and outcomes.
- The facilitators and barriers reported by patients who attempted to discontinue are in accordance with and support previous findings from the qualitative literature.
- Professionals' perspectives were included to triangulate patients' perspectives on discontinuation of ADM in the qualitative study.
- Reports of relapse/recurrence may have been inflated by withdrawal or post-withdrawal symptoms, which could not be differentiated with the available data.
- Selection bias cannot be ruled out, as participation in the trial might have been influenced by perceptions and preferences regarding both mindfulness and the use of antidepressant medication.

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent mental disorder with a large burden of disease and high risk of recurrence.[1] One of the most commonly used and effective relapse prevention strategies is maintenance antidepressant medication (ADM).[2] Current guidelines recommend patients with MDD to continue medication for at least two years after remission.[3 4] However, patients are often reluctant to use ADM for long periods because of side effects, pregnancy, or interaction with other medication. As discontinuing ADM can be associated with significant withdrawal effects,[5] and increased relapse risk,[6] there has recently been a rise in scientific and clinical interest in this area.[7 8] One of the psychological treatment strategies that have been developed to protect against depressive relapse is Mindfulness Based Cognitive Therapy (MBCT).[9] A recent meta-analysis showed that MBCT is at least as effective in reducing the risk of relapse/recurrence as ADM.[10] As MBCT provides patients support in managing uncomfortable somatic sensations and emotions, it could also help them to deal with possible withdrawal effects and increased emotional reactivity during discontinuation of ADM.[7 11] Two randomized controlled trials (RCTs) in the UK, offering recurrently depressed patients MBCT with additional tapering support, indeed showed successful tapering of ADM in about three quarter of their participants.[12 13] However, studies conducted in the Netherlands showed markedly lower levels of successful tapering, i.e. about half when combined with MBCT[6] or Preventive Cognitive Therapy[14] and only 6% when tapering advise was given without further support.[15]

The current study describes secondary analyses of an RCT, in which 249 patients with recurrent depression in remission were randomly allocated to MBCT with continued use of ADM (n=121), or to MBCT followed by discontinuation (n=128). Results showed that discontinuing ADM after MBCT was associated with significantly higher relapse rates than continuing ADM after MBCT (intent-to-treat: 54% versus 39%, per-protocol: 69% versus 46%, respectively). 6 In the original MBCT+discontinuation treatment arm, only 53% of the participants were able to fully discontinue within six months from baseline, 13% discontinued partially, 25% of the participants decided to continue their medication as it was despite the randomization, and for 9% it was unknown. Notably,

discontinuation also occurred in patients asked to continue their medication: 12% discontinued fully and 14% partially.

The aim of this study was to examine possible predictors and outcomes of full, partial and no discontinuation of ADM in recurrently depressed individuals who participated in MBCT in the context of the abovementioned RCT. In addition, we explored the barriers and facilitators of discontinuation by conducting in-depth qualitative interviews with a subsample of RCT participants and their attending clinicians.

METHODS

Data

Data originated from an RCT comparing MBCT followed by discontinuation or continuation of ADM.[6] For the current paper, groups were created post hoc based on patients' actual discontinuation profiles during the study, i.e. full, partial, or no discontinuation of their ADM. Quantitative data were collected between September 2009 and June 2013.

We invited a purposive sample of the participants and their attending clinicians for a semi-structured interview focussing on barriers and facilitators of discontinuation. These interviews were conducted after the trial (May and August 2013) as a follow-up study specifically focusing on the barriers and facilitators of ADM discontinuation.

Participants

Patients with three or more previous depressive episodes who had been using ADM for 6 months or longer were recruited in 12 secondary and tertiary psychiatric outpatient clinics across the Netherlands between September 2009 and January 2012. For further information on the specific in- and exclusion criteria and process of obtaining informed consent from participants we refer to the publication of the

trial itself.[6] The study was approved by the Medical Ethics Committee Arnhem-Nijmegen (nr. 2008/242).

Public and Patient Involvement

At the time of the study, public or patients were unfortunately not yet involved in working with the research funder to prioritise research or offering advice as members of our own project steering group. However, patients and health care professionals in the participating centres were regularly informed about the progress of the study via newsletters. In addition, the qualitative feedback on the barriers and facilitators of MBCT as supportive intervention during discontinuation of ADM has been directly translated into the refinement of an MBCT intervention to support ADM discontinuation, investigated in an RCT conducted between 2015 and 2019 by our group.[16]

Procedure

A detailed description of the study procedures in line with CONSORT guidelines is provided in the RCT report.[6] Eligible patients were randomly assigned to MBCT followed by guided discontinuation of ADM or to MBCT with continuation of ADM. Follow-up quantitative assessments (measures of depression, relapse/recurrence, ADM usage) took place 3, 6, 9, 12, and 15 months after baseline.
For the qualitative part of the study, we adhered as much as possible to the Standards for Reporting Qualitative Research (SRQR).[17] A subset of 15 participants from the MBCT+Discontinuation group were purposively sampled on the basis of age, sex, and discontinuation profile (i.e. fully, partially or not discontinued). We kept inviting participants until saturation of the data was established. For the purpose of triangulation, we also included physicians who had guided discontinuation. Interviews were semi-structured, individual and by telephone. Patients and attending physicians were asked the following questions: 1) “How did the tapering go?”, 2) What expectations did you have about tapering ADM?”, 3) “What hampered your (the patients’) discontinuation process?”; 4) “What facilitated your (the patients’) discontinuation process?”; 5) “What was the role of mindfulness in your (the patients’)

process of discontinuation?" and 6) "Do you have any suggestions for future guidance on tapering ADM?". The interviews were conducted by CW and ES, both female. CW was a graduate student in Psychology during the interviews and data analysis, and a psychologist and PhD student researching ADM discontinuation in primary care at the time of writing. ES was a medical student completing her research internship. Neither of them were acquainted with the participants prior to the interviews.

Interventions

Mindfulness-Based Cognitive Therapy (MBCT)

MBCT was largely based on the protocol by Segal, Williams, and Teasdale[9] and consisted of eight weekly sessions of 2.5 hours and one day of silent practice between the sixth and seventh session. It was delivered in groups of eight to 12 participants and included mindfulness meditation practices, group inquiry, cognitive-behavioural elements, interactive psycho-education, and home practice.

Discontinuation or continuation of ADM

Patients in the discontinuation arm were asked and recommended to gradually withdraw from their ADM over a period of five weeks, starting after the seventh session of MBCT, with specified steps for each of the commonly used types of antidepressants[18] and supervised by their attending physician (mostly psychiatrists) in three to 12 consultations. Patients in the continuation arm were offered a minimum of one consultation. Psychiatrists were instructed to maintain or reinstate an adequate dose of ADM, and recommendations to manage side effects were provided. Full discontinuation was defined as tapering to nil milligrams within six months after baseline. Partial discontinuation was defined as tapering to a lower dose and 'no discontinuation' was defined as maintaining or increasing the initial therapeutic dose of ADM throughout the first six months after baseline.

Outcome measures

Relapse/recurrence rates were compared between the three discontinuation subgroups (full, partial, not). It was assessed using the Structured Clinical Interview for DSM-IV[19] (SCID) 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). Baseline severity of depressive symptoms was measured with the Inventory for Depressive Symptomatology (IDS-C).[20]

Statistical and qualitative analysis

Quantitative analysis

All analyses were performed using SPSS Statistics version 20.0. Probability values lower than 0.05 (two-tailed) were considered significant for all analyses. Possible differences in baseline characteristics between participants who discontinued fully, partially or not at all were examined using independent samples t-tests for continuous and Pearson χ^2 tests for categorical variables.

Relapse/recurrence rates across the entire trial sample, differentiated into three discontinuation profile groups (full, partial, not) were compared with a Pearson χ^2 test and differences in time to relapse/recurrence were analysed using a Cox regression proportional hazards model. Baseline depression severity and number of previous episodes (log transformed) were included as covariates because these factors have been consistently associated with an increased relapse risk.[21] 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.

Qualitative analysis

The qualitative interviews were audio-taped, transcribed verbatim en imported in the scientific qualitative research software program ATLAS.ti (version seven). [22]We used a thematic approach to analyze the data, with a focus on barriers and facilitators of the discontinuation process, including previous expectations and the possible role of mindfulness in that process. The underlying framework for the study can be described as a combination of a phenomenological and praxis-oriented approach,

as we were both interested in participants' views and in behavioural strategies that helped or hindered discontinuation. Analysis started as soon as the first data were collected and continued with each additional interview. Two researchers (CW, ES) coded the transcripts independently to minimize subjectivity. Subsequently codes were modified and categorized as various facilitators and barriers by the full research team, also consisting of a professor of psychiatry and mindfulness teacher with prior experience with qualitative research (AS) and a psychologist and post-doc researcher who also worked as a mindfulness teacher (MH). The cycle of comparison and reflection on "old" and "new" themes was repeated several times. Eventually, characteristic quotes were used to illustrate the final themes and subthemes. The original Dutch quotes in this article were translated into English by the authors.

RESULTS

Quantitative results

Flow of ADM discontinuation and intervention adherence

The flow of participants and their ADM use is shown in Figure 1. Of the 249 participants randomized, 128 were allocated to MBCT+Discontinuation and 121 to MBCT+ADM. From 23/249 (9%) patients, we had insufficient information about ADM use due to early dropout. Consequently, descriptive and statistical analyses were performed on 226 participants.

Of the 82 patients who fully discontinued ADM within six months after baseline, 41 (50%) restarted ADM at some point during the 15-month study period. Based on the SCID interviews, this might have been related to a relapse in 31/41 (76%) of them.

Adherence to MBCT sessions differed significantly between those with a full discontinuation profile M=7.2 ± 1.5 versus the no discontinuation group, M=6.4 ± 2.0 (p = .003). Those who partially discontinued were in between, with an attendance of M=7.0 ± 1.4. The number of medication consultations also differed significantly among the groups, being highest for those with a full discontinuation profile (M=3.0 ± 2.0; range 0-13) versus partial discontinuation (M=2.3 ± 1.4; range

1-6) (p = .03) versus no discontinuation group (M=1.6 ± 1.5; range 0-11) (p < .00). The partial and full discontinuation group did not differ significantly (p = .06).

[Figure 1]

Demographic and clinical characteristics

The demographic and clinical characteristics for the different profile groups are summarized in Table 1. In comparison with those who did not discontinue, females were more likely to fully discontinue than men (76% versus 53%; p = 0.026) and employed participants more likely than those who were unemployed (78% versus 56%; p = 0.002). Those who fully discontinued also had significantly less depressive symptoms at baseline than those who did not (M=10.9 (SD 8.8) vs M=14.4 (SD 10.6), p = 0.018; d = 0.37).

Table 1. Baseline demographic and clinical characteristics of 226 patients with recurrent depression receiving mindfulness-based cognitive therapy who subsequently engaged in full, partial, or no discontinuation of maintenance antidepressant medication (adapted from Huijbers et al, 2016).

	Total N = 226 [a]						
Variable	**Full discontinuation (n = 110)**		**Partial discontinuation (n = 34)**		**No discontinuation (n = 82)**		**Sig.**
	N	%	N	%	N	%	*p*
Female	62	76	18	53	71	64	**0.048**
Educational level							0.421
-Low	7	9	3	9	6	6	
-Middle	24	29	10	29	31	28	
-High	49	60	21	62	64	58	
-Missing	2	2	0	0	9	8	
Marital status							0.560
-Single	19	23	6	18	27	25	
-Married/cohabiting	46	56	22	65	60	55	
-Divorced/widowed	15	18	6	18	16	15	
-Missing	2	2	0	0	7	6	
Employed [(n=225)]	63	78	22	65	62	56	**0.009**

Remission							0.069
-Full, IDS-C ≤ 11	51	62	17	50	50	45	
-Partial, IDS-C > 11	31	38	17	50	60	55	
Type of mADM							0.669
-SSRI	64	78	23	68	21	19	
-TCA	13	16	7	21	21	19	
-Other [b]	5	6	4	12	6	6	
Previous CBT treatment	45	55	21	62	68	62	0.595
Suicide attempt (lifetime)	18	22	12	15	21	49	0.429
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	50.0	11.1	52.0	9.8	51.0	10.3	0.507
Baseline depression (IDS-C)	10.9	8.8	12.7	11.2	14.4	10.6	0.059
Nr. previous episodes	5.6	4.9	7.4	8.0	5.7	3.9	0.167
Age at MDD onset [(n=219)]	27	11.9	25	10.8	25.0	12.3	0.388

Legend: IDS-C, Inventory of Depressive Symptomatology – Clinician rated; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; CBT, cognitive-behavioural therapy; MDD, major depressive disorder.

[a] Excluding 23 of the original 249 trial participants due to missing data regarding discontinuation.

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

Relapse and recurrence

Rates of relapse were 66% for full discontinuation, 38% for partial discontinuation and 45% for no discontinuation. As illustrated in Figure 2, Cox regression analysis with baseline level of depression and number of previous episodes (log transformed) as covariates showed that there were significant differences in terms of risk of relapse across the three groups (p = 0.02). Compared with the full discontinuation group, those who did not discontinue had a lower risk of relapse (hazard ratio = 0.67; 95% CI = 0.45 – 0.99; p = 0.04). The lowest risk of relapse was seen for those who partially discontinued, compared with full discontinuation (hazard ratio = 0.47; 95% CI = 0.26 – 0.87; p = 0.02). There was no significant difference in relapse risk between partial and no discontinuation (p = 0.27).

[Figure 2]

Qualitative results

The interviewed patients consisted of eight women and nine men, with a mean IDS-score at baseline of 11 ± 7.8. See Table 2 for their characteristics. Nine patients discontinued their ADM fully, three partially and three did not discontinue their ADM. The time elapsed between the final trial assessment and the qualitative interview was 0 – 23 months (Mn=11 months ± 6).

Table 2. Patients' characteristics for the subset of participants in the qualitative study.

Patient	Sex	Age range	IDS at baseline	Discontinuation ≤6 months	Relapse ≤15 months
P1	male	30-39	9	Partially	No
P2	male	40-49	15	Not	No
P3	female	30-39	10	Fully	Yes
P4	female	20-29	10	Fully	Yes
P5	male	60-69	0	Fully	Yes
P6	female	50-59	13	Partially	Yes
P7	male	70-79	10	Fully	No
P8	female	50-59	17	Partially	Yes
P9	male	50-59	3	Not	Yes
P10	male	60-69	30	Fully	Yes
P11	female	60-69	20	Not	Yes
P12	female	50-59	7	Fully	Yes
P13	male	50-59	14	Fully	No
P14	female	30-39	14	Fully	Yes
P15	female	60-69	0	Fully	No

Five themes emerged from the patient interviews: I) patients' pre-existing beliefs about depression, medication and tapering; II) current experience with antidepressants; III) psychosocial conditions and physical problems; IV) clinical support and V) participating in MBCT. The most significant subthemes are described in more detail below. See online supplement 1 for an overview of themes, subthemes and illustrating quotes.

I. Pre-existing beliefs about depression, medication and tapering

Facilitators

Being aware that others are also subject to periods of low mood and feeling downhearted occasionally seemed to facilitate the process of discontinuation. This was accompanied by the realization that medication is not always needed to suppress those feelings. Although most respondents had regarded their medication as helpful during their depression, some patients considered taking pills for long periods of time as unhealthy and even 'harmful'. Respondents also talked about their wish to manage without pills.

Barriers

Several respondents mentioned that they were (told to be) missing a specific substance in their brain and therefore needed ADM. They considered their condition as chronic and medication as necessary. Not surprisingly, these people were reluctant to (fully) taper their medication. Another central theme was the fear of relapse in depression. Several patients expressed concern that this would happen. On a related note, many participants had tried to come off medication in the past and experienced difficulties, i.e. withdrawal symptoms.

II. Current experience with antidepressants

Facilitators

There were patients describing uncertainty about the benefits of taking their medication. In addition, the occurrence of unwanted or 'side' effects emerged as a theme. In addition, being able to adopt a personalized tapering schedule facilitated the discontinuation process. Such a personalized schedule typically contained adaptations with regard to the duration and magnitude of the dose reductions, or were much more flexible so that tapering could be guided by their own mental health state.

Barriers

Some participants for whom ADM were still beneficial in managing depressive symptoms did not start discontinuation. Withdrawal effects appeared one of the major reasons to interrupt discontinuation,

restart or increase the dose of medication. For many patients the tapering speed according to the RCT guideline was considered too fast. One patient said, for example: "*I was using Citalopram and I believe I had to taper within 2 weeks, but I was suffering quite a lot from withdrawal symptoms, so therefore, after consultation, tapered somewhat more slowly.*"

III. Life circumstances

Facilitators

In a relatively quiet period, people appeared more likely to start and proceed with tapering.

Barriers

If there were stressful circumstances (for example, work-related problems), a lack of support from family or friends, or health problems, people seemed more reluctant to start or continue the tapering process.

IV Clinical support

Facilitators

Availability and accessibility of professional guidance was an important facilitator, both before and during the tapering process. Patients mentioned the importance of bringing in their own ideas of how clinical support would ideally look like, and having the freedom to choose for themselves what they felt was best. Reassurance about being able to restart medication in case of deterioration was also described as helpful.

Barriers

In some cases the attending clinician would advise against discontinuation, which was mentioned as a barrier: "*He [the psychiatrist] said: "I would not do it with your history and family matters". But I*

wanted to taper (..) and so I did.". Another barrier that emerged from the interviews was the impression that, possibly related to the context of the RCT, tapering was mandatory.

V. Mindfulness practice

Facilitators

Participants mentioned peer support in MBCT as a facilitating factor. Witnessing how other people deal with similar problems and sharing fears and insecurities about tapering were regarded as helpful and reassuring. In addition, mindfulness itself had been a source of support during tapering, for example being able to distinguish feelings of stress from a depressive relapse and recognizing that these were triggered by difficult psychosocial circumstances, which did not necessarily require to restart medication. Mindfulness practice also provided an alternative method to prevent depressive relapse, by recognizing periods of increased vulnerability and using other approaches rather than increasing the dose of ADM (e.g. daily walks in nature, seeing friends and reducing workload).

Barriers

The MBCT group context could also negatively impact the process. MBCT groups included participants from both arms of the RCT, including those who were asked to continue ADM after MBCT. It was mentioned that sometimes fellow group members, who continued their medication, advised against discontinuation.

Facilitators and barriers as reported by attending clinicians

Fourteen patients gave permission to interview their attending physician, of whom seven were willing and able to participate. See Table 3 for their characteristics.

Table 3. Professionals' characteristics.

Professional	Sex	Age range	Function	Institute
PF1	female	50-59	psychiatrist	university medical center
PF2	female	30-39	psychiatrist in training	university medical center
PF3	female	40-49	psychiatrist	mental health institute
PF4	female	40-49	physician	university medical center
PF5	male	60-69	psychiatrist	private practice
PF6	female	50-59	psychiatrist	university medical center
PF7	male	40-49	psychiatrist	mental health institute

Professionals' perspectives generally showed a large overlap with the views expressed by participants. For example, the benefits of tapering slowly and with a personalized tapering scheme clearly emerged from these interviews. In terms of barriers, the pivotal roles of negative experiences with tapering in the past, worrying about symptoms and possible relapse, and stressful circumstances were mentioned.

Some different themes emerged from these interviews as well. Clinicians reported feeling reluctant to discontinue ADM because of their own worries about patients having a relapse, especially in case of a long psychiatric history or comorbidity. They spoke more specifically about ADM characteristics (half-life time) and switching to a different type of ADM before fully discontinuing as a possible facilitator. They also mentioned the possible use of other psychological interventions to help patients cope with emerging symptoms. Regarding barriers, clinicians were particularly concerned about nocebo effects when discussing potential withdrawal effects, suggesting to provide some information but avoiding being very specific about it.

DISCUSSION

Principal findings

The current paper provides quantitative post-hoc data from an RCT, describing the flow, characteristics and outcomes of patients with recurrent depression who discontinued ADM fully, partially or not at all. Quantitative data were complemented by qualitative data on the barriers and facilitators of ADM withdrawal. Remarkably, there were relatively low rates of adherence to the ADM protocol, including crossover. These non-compliance rates and apparent difficulties with discontinuation are in line with previously published studies on (preventive) cognitive therapy for recurrently depressed patients[23] and anxiety disorders.[24]

However, two UK studies with a MBCT+discontinuation arm[12 13] found much better discontinuation and relapse rates. Some possible explanations for these differences deserve attention. First, the UK studies were conducted in a primary care setting and ours in secondary care. Discontinuation of ADM in secondary care may be more challenging due to longer and more complicated psychiatric, and possibly medical, histories. In addition, the role of health care professionals might be different: GPs who guided discontinuation in the UK may have offered their patients a more psychologically-oriented framework for understanding depression whereas psychiatrists in the Netherlands may have offered a more biologically oriented one. In fact, some of them appeared to have actively advised against discontinuation. In our trial patients participated in mixed MBCT groups also including patients continuing their ADM, so guided tapering took place outside the MBCT context. In the UK-based studies, MBCT groups were homogeneous, allowing the tapering process to be a more integrated part of the training.

It is important to keep in mind that the analyses of the current study are not based on the original intervention and control conditions, but on the actual ADM continuation or discontinuation in the entire study population. In terms of predictors, full discontinuation occurred more frequently in women, and in those who were employed. Indeed, the qualitative data point to psychosocial stressors as possible barriers to discontinuation, and problems with finding or holding on to a suitable job might be one of them. Residual symptoms of depression may be a predictor of discontinuation too: levels of baseline depression were lower in the full versus no discontinuation group. . In contrast, the qualitative data suggest that if ADM are considered an effective treatment to reduce or manage depressive symptoms, patients are *less* likely to taper, and vice versa. Possibly, these beliefs may vary over time

and across circumstances. For example, a patient who considers tapering because ADM has not been very effective, but would nevertheless postpone this because of a current episode of depression. Aside from baseline depression levels, post hoc analyses by Kuyken et al [12] suggested that patients with a more severe psychiatric history (earlier age of onset and greater severity of the last episode) were *more* likely to taper their ADM after MBCT. In the current study, age at onset was no predictor of successful discontinuation, neither was the number of previous episodes. The relation between clinical characteristics and discontinuation appears to be a complex interplay between several other factors [25].

Even in those participants who discontinued completely in the current study, more than half restarted medication within the next nine months, possibly related to relapse or recurrence of depression. Relapse rates were indeed substantially higher for fully discontinued patients than for partially and not discontinued. These differences seem clinically relevant, and may even advocate partial rather than full discontinuation. While linear tapering regimes are commonplace, the most challenging part of the withdrawal process may occur at the lowest doses. As this might have to do with hyperbolic dose-response relationships between drugs such as selective serotonin reuptake inhibitors and their receptor,[26] it has been suggested that "stop slow if you go low" regimes may help to minimize withdrawal symptoms.[27] Although the use of "tapering strips" can be a suitable way to taper gradually,[28] for many types of ADM these are not yet available.

In line with a recent systematic review,[25] worry and fear of relapse emerged as clear barriers to discontinuation in the qualitative interviews. These fears appear to exist not only for patients, but also for attending physicians. Some professionals reported being anxious about responsibility for deterioration and sometimes feeling unable to help, which has also been reported in previous studies.[29] For both patients and professionals, accessibility and availability of support during tapering is important.

Strengths and weaknesses

A major strength of the current study is that we combined quantitative and qualitative data to investigate what makes it more difficult or easy to discontinue ADM. Rather than using opinions or

hypothetical perspectives on tapering, we report data on the actual tapering process in an RCT, including clinical outcomes, in which full, partial and no discontinuation were defined before the study started [18]. In addition, we looked at professionals' perspectives to triangulate patients' perspectives on discontinuation of ADM in the qualitative study.

One of the limitations of the current study is that reports of relapse/recurrence may have been inflated by withdrawal or post-withdrawal symptoms. Chouinard and Chouinard have developed criteria permitting identification of three types of withdrawal problems associated with SSRIs: new withdrawal symptoms, rebound and persistent post withdrawal disorder, which can be differentiated from relapse and recurrence.[30] As withdrawal symptoms were not included as an outcome measure, we could unfortunately not differentiate this in our RCT.

Another limitation is that there is no control group of patients withdrawing from ADM without MBCT. Consequently, predictors of discontinuation of antidepressants with MCBT might be predictors of the take up of MCBT rather than discontinuation of ADM. The same issue might may apply to the discontinuation outcomes. These issues might be conflated by the differences found in attendance at MCBT sessions. Although we did collect some baseline demographic and clinical characteristics that might influence discontinuation, this obviously does not include all the factors that a prescribing clinician would consider before recommending discontinuation. For instance there are no measures of patient's subjective readiness to discontinue, mental and physical comorbidity or other baseline medication which might lead to adverse effects on the patient. This is a limitation of predictors of discontinuation and may confound those factors that have been identified as well as outcome. These factors may also be important to understand why there might be differences in outcome with MCBT on ADM discontinuation across studies.

In addition, we cannot rule out selection bias, as participation in the trial might have been influenced by perceptions of both mindfulness and ADM. Participants in the qualitative part of the study may be more positive about MBCT than those who dropped out of the intervention. In addition, given the delay between ADM discontinuation and the qualitative interview, memory bias may have occurred with regard to its barriers and facilitators. In addition, although we specifically asked about patients' experiences within the trial, their responses appeared to also include previous and later

experiences. Moreover, the number of professionals contributing to the qualitative interview data was rather small.

Clinical recommendations

First and foremost, our findings clearly point to the necessity of up-to-date, accessible and professional guidance for those who wish to come off their ADM. A recently published shared decision making tool[31] might assist patients and their clinicians in their consultations. Secondly, a personalized tapering approach seems essential to enable successful tapering. With accumulating evidence suggesting that slow tapering is associated with better outcomes,[32] it is important to slow down the pace of tapering on the basis of patients' preferences and needs. Finally, results from the current study point to the possible clinical relevance of tapering to low doses of ADM rather than complete withdrawal. This might prevent withdrawal symptoms, whether neurochemical or psychological, empower patients by letting them choose their optimal dose, and reduce side effects and health care costs.

Research implications

So far, it remains unclear whether the increased risk of relapse and withdrawal symptoms are a direct effect of neurobiological changes, or an indirect effect driven by psychological mechanisms such as fear of relapse, negative expectations based on previous failed tapering attempts, or nocebo effects caused by information about withdrawal symptoms. To disentangle these effects at a more fundamental level, a double-blind withdrawal study with active versus placebo pills should be conducted.

In addition, future research might focus on the effectiveness of protocolized tapering support interventions and existing psychological interventions that might be helpful to manage withdrawal symptoms and depression. Besides MBCT, Preventive Cognitive Therapy might be a valuable option.[14] Future studies should include homogeneous groups of patients who are all in the same phase of discontinuation. We are currently conducting an RCT in primary care inviting long-term ADM

users who have made a shared decision to discontinue, are supported by mental health assistants or their GP in devising and monitoring their tapering process, and are either offered additional MBCT or not.[16]

Funding statement

The RCT from which data were drawn was funded by ZonMW, the Netherlands Organization for Health Research and Development (Grant no. 170992903 awarded to Prof. A.E.M. Speckens). No additional funding was requested for the current mixed-methods study. The funder had no role in the writing of the manuscript or the decision to submit it for publication.

Data sharing

We aim to make our data available for other researchers as much as possible, albeit with a restricted access policy. As data are currently not yet filed in a public repository, researchers interested in re-using our data are invited to contact the authors.

Competing interests

MH and AS report grants from ZonMW Doelmatigheid, during the conduct of the study; CW, ES and JS have nothing to disclose.

Author contributions

MH and AS led the RCT from which the quantitative data were drawn. For the current study, MH, CW, JS and AS formulated the study design. MH and CW collected data. ES assisted with data collection. MH and CW contributed to data analysis and data interpretation. MH wrote the manuscript and prepared the figures and tables. CW, ES, JS and AS edited the manuscript.

Acknowledgements

The authors would like to acknowledge all participants who have contributed to this work, as well as all health care professionals who have participated in the trial and those who contributed to the qualitative interviews.

REFERENCES

1. Richards D. Prevalence and clinical course of depression: a review. *Clinical psychology review* 2011;31(7):1117-25. doi: 10.1016/j.cpr.2011.07.004 [published Online First: 2011/08/09]
2. Gueorguieva R, Chekroud AM, Krystal JH. Trajectories of relapse in randomised, placebo-controlled trials of treatment discontinuation in major depressive disorder: an individual patient-level data meta-analysis. *The lancet Psychiatry* 2017;4(3):230-37. doi: 10.1016/s2215-0366(17)30038-x [published Online First: 2017/02/13]
3. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (3rd ed.): APA, 2010.
4. National Institute for Health and Care Excellence. Depression in adults: recognition and management. CG90. London: NICE, 2009.
5. Davies J, Read J. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? *Addictive behaviors* 2019;97:111-21.
6. Huijbers MJ, Spinhoven P, Spijker J, et al. Discontinuation of antidepressant medication after mindfulness-based cognitive therapy for recurrent depression: randomised controlled non-inferiority trial. *British Journal of Psychiatry* 2016;208(4):366-73. doi: 10.1192/bjp.bp.115.168971
7. Maund E, Stuart B, Moore M, et al. Managing Antidepressant Discontinuation: A Systematic Review. *Annals of family medicine* 2019;17(1):52-60. doi: 10.1370/afm.2336 [published Online First: 2019/01/24]
8. Bowers HM, Kendrick T, Glowacka M, et al. Supporting antidepressant discontinuation: the development and optimisation of a digital intervention for patients in UK primary care using a theory, evidence and person-based approach. *BMJ Open* 2020;10(3):e032312. doi: 10.1136/bmjopen-2019-032312 [published Online First: 2020/03/11]
9. Segal, Williams JMG, Teasdale JD. Mindfulness-Based Cognitive Therapy for Depression, 2nd edn.: Guilford Press 2012.
10. Kuyken W, Warren FC, Taylor RS, et al. Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse: An Individual Patient Data Meta-analysis From Randomized Trials. *JAMA Psychiatry* 2016;73(6):565-74. doi: 10.1001/jamapsychiatry.2016.0076 [published Online First: 2016/04/28]
11. Tickell A, Byng R, Crane C, et al. Recovery from recurrent depression with mindfulness-based cognitive therapy and antidepressants: a qualitative study with illustrative case studies. *BMJ Open* 2020;10(2):e033892. doi: 10.1136/bmjopen-2019-033892 [published Online First: 2020/02/23]
12. Kuyken W, Byford S, Taylor RS, et al. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. *J Consult Clin Psychol* 2008;76(6):966-78. doi: 10.1037/a0013786 [published Online First: 2008/12/03]
13. Kuyken W, Hayes R, Barrett B, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. *Lancet* 2015;386(9988):63-73. doi: 10.1016/S0140-6736(14)62222-4 [published Online First: April 21, 2015]
14. Bockting CL, Klein NS, Elgersma HJ, et al. Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. *The Lancet Psychiatry* 2018;5(5):401-10.
15. Eveleigh R, Muskens E, Lucassen P, et al. Withdrawal of unnecessary antidepressant medication: a randomised controlled trial in primary care. *BJGP Open* 2018;1(4):bjgpopen17X101265.
16. Wentink C, Huijbers MJ, Lucassen P, et al. Discontinuation of antidepressant medication in primary care supported by monitoring plus mindfulness-based cognitive therapy versus

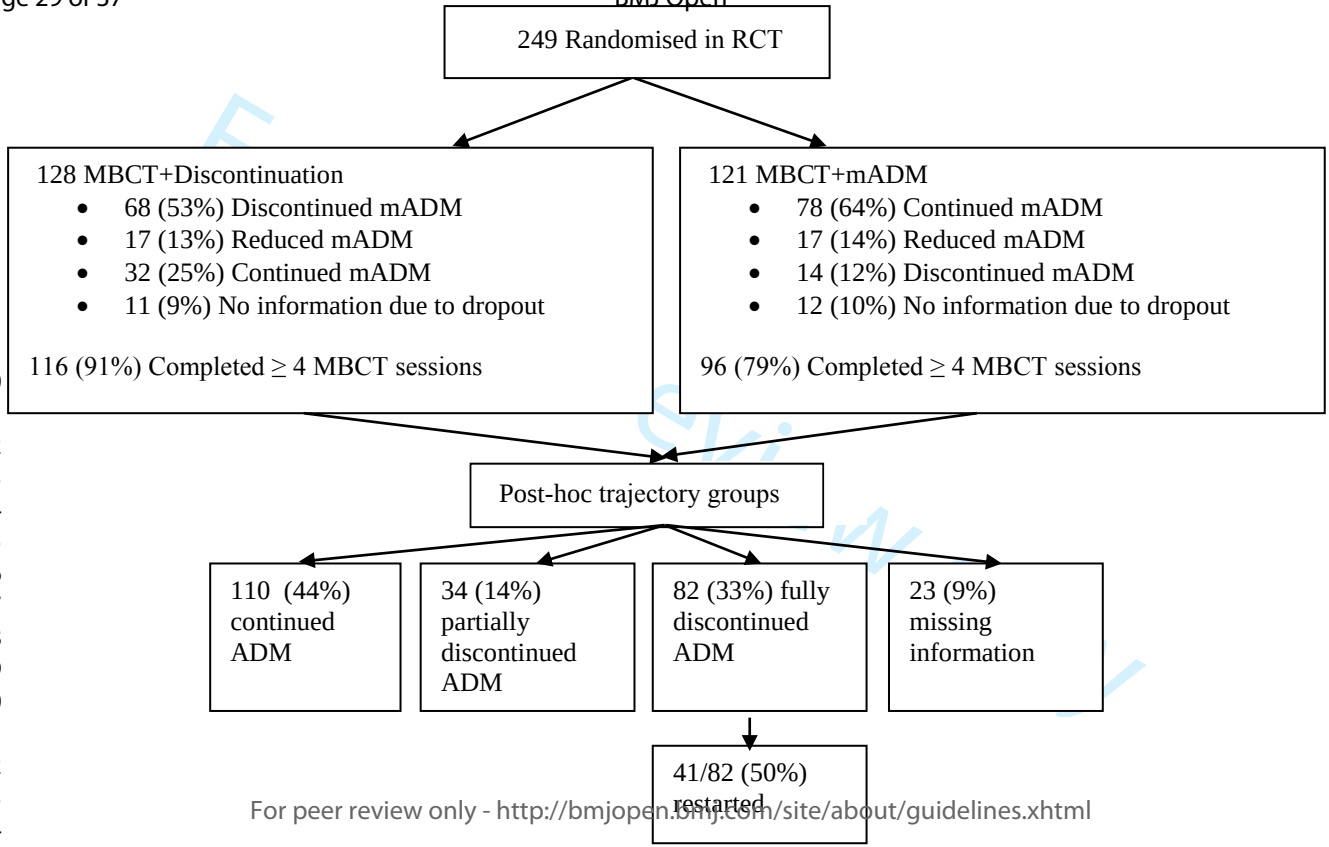
monitoring alone: design and protocol of a cluster randomized controlled trial. *BMC family practice* 2019;20(1):105.
17. O'Brien BC, Harris IB, Beckman TJ, et al. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med* 2014;89(9):1245-51. doi: 10.1097/acm.0000000000000388 [published Online First: 2014/07/01]
18. Huijbers MJ, Spijker J, Donders AR, et al. Preventing relapse in recurrent depression using mindfulness-based cognitive therapy, antidepressant medication or the combination: trial design and protocol of the MOMENT study. *BMC Psychiatry* 2012;12(1):125. doi: 10.1186/1471-244x-12-125 [published Online First: 2012/08/29]
19. First MB, Gibbon M, Spitzer RL, et al. User's guide for the structured clinical interview for DSM-IV axis I Disorders—Research version. *New York: Biometrics Research Department, New York State Psychiatric Institute* 1996
20. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): Psychometric properties. *Psychol Med* 1996;26(3):477-86.
21. Hardeveld F, Spijker J, De Graaf R, et al. Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatr Scand* 2010;122(3):184-91. doi: 10.1111/j.1600-0447.2009.01519.x [published Online First: 2009/12/17]
22. Boeije H. A purposeful approach to the constant comparative method in the analysis of qualitative interviews. *Quality and quantity* 2002;36(4):391-409.
23. Bockting CLH, Klein NS, Elgersma HJ, et al. Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. *The lancet Psychiatry* 2018;5(5):401-10. doi: 10.1016/s2215-0366(18)30100-7 [published Online First: 2018/04/08]
24. Scholten WD, Batelaan NM, van Oppen P, et al. The Efficacy of a Group CBT Relapse Prevention Program for Remitted Anxiety Disorder Patients Who Discontinue Antidepressant Medication: A Randomized Controlled Trial. *Psychotherapy and psychosomatics* 2018;87(4):240-42. doi: 10.1159/000489498 [published Online First: 2018/06/04]
25. Maund E, Dewar-Haggart R, Williams S, et al. Barriers and facilitators to discontinuing antidepressant use: A systematic review and thematic synthesis. *Journal of affective disorders* 2019;245:38-62. doi: 10.1016/j.jad.2018.10.107 [published Online First: 2018/10/27]
26. Meyer JH, Wilson AA, Sagrati S, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. *Am J Psychiatry* 2004;161(5):826-35. doi: 10.1176/appi.ajp.161.5.826 [published Online First: 2004/05/04]
27. Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. *The lancet Psychiatry* 2019;6(6):538-46. doi: 10.1016/s2215-0366(19)30032-x [published Online First: 2019/03/10]
28. Groot PC, van Os J. Antidepressant tapering strips to help people come off medication more safely. *Psychosis* 2018;10(2):142-45. doi: 10.1080/17522439.2018.1469163
29. Bowers HM, Williams SJ, Geraghty AWA, et al. Helping people discontinue long-term antidepressants: views of health professionals in UK primary care. *BMJ Open* 2019;9(7):e027837. doi: 10.1136/bmjopen-2018-027837 [published Online First: 2019/07/07]
30. Chouinard G, Chouinard VA. New Classification of Selective Serotonin Reuptake Inhibitor Withdrawal. *Psychotherapy and psychosomatics* 2015;84(2):63-71. doi: 10.1159/000371865 [published Online First: 2015/02/28]
31. Wentink C, Huijbers MJ, Lucassen PLBJ, et al. Enhancing shared decision making about discontinuation of antidepressant medication: a concept-mapping study in primary and secondary mental health care. *British Journal of General Practice* 2019 doi: 10.3399/bjgp19X706001

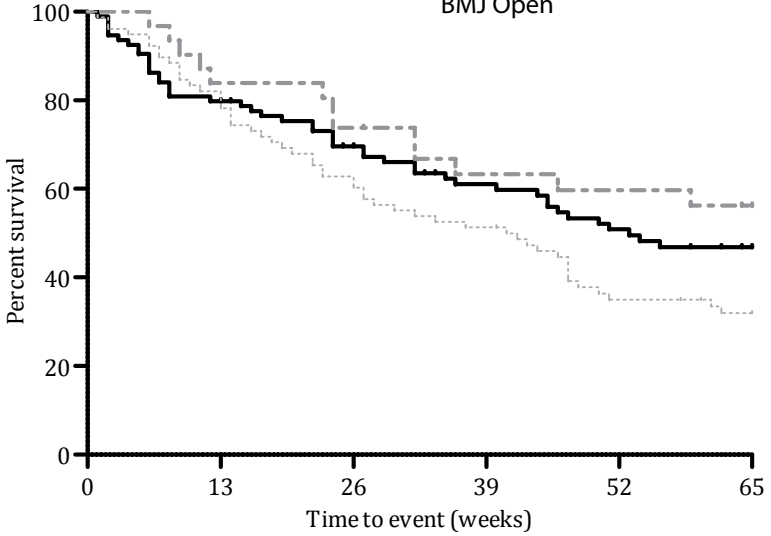
32. Baldessarini RJ, Tondo L, Ghiani C, et al. Illness risk following rapid versus gradual discontinuation of antidepressants. *The American journal of psychiatry* 2010;167(8):934-41. doi: 10.1176/appi.ajp.2010.09060880 [published Online First: 2010/05/19]

Figure captions

Figure 1. Flow chart of participants, their adherence to mindfulness-based cognitive therapy (MBCT) and their use of antidepressant medication (ADM).

Figure 2. Survival curves over 15-month follow up for risk of relapse in recurrently depressed patients with different profiles of discontinuing antidepressant medication: fully (n=82), partially (n=34) or not (n=110).





Number at risk

No discont.	110	74	59	48	38	0
Partial discont.	34	25	22	18	17	0
Full discont.	82	61	47	40	25	0

Online supplement 1. Facilitators and barriers in the discontinuation of antidepressant medication as experienced by patients with recurrent depression who had participated in an MBCT course. Most subthemes are illustrated with quotes in italic.

THEMES	FACILITATORS TO DISCONTINUATION	BARRIERS TO DISCONTINUATION
I Pre-existing beliefs		
About depression	Common humanity *"I noticed that I, well, that I am not always feeling that cheerful. And I have accepted myself as such by now, this is who I am" (woman, 50-59, partially discontinued)*	Missing substance in the brain *"So I thought, well there is just something wrong in your brain and you will have to learn to live with that" (man, 60-69, fully discontinued, describing a previous experience)*
About medication	ADM as harmful *"Yes actually I wanted to get rid of that junk. I call it junk now, but of course it is a beautiful invention, glad that it exists, but I still think .. well, if I can do it without pills." (man, 50-59, not discontinued)* Dependency as weakness *"I want to be able to do it myself. It also felt somewhat like a weakness, that you would need a pill to feel reasonably well" (woman,20-29, fully discontinued)*	Accepting long-term use *"At a certain moment I thought well, life without medication, well for some people this could be an option I guess, but not for me." (man, 30-39, partially discontinued)*
About tapering	Open mind *"I actually noticed very soon that I benefited from the exercises. Then I thought, consider I start withdrawing and I then have a relapse. (…) But on the other hand, I already felt so much better that I thought: well, who knows? I just see what will happen." (man, 60-69, fully discontinued)*	Fear of relapse in depression *"That you relapse into a more severe depression than before (..) And I have had such an experience and did not want to go through that again." (woman, 50-59, partially discontinued)* Previous negative experiences with withdrawal effects during tapering

		"With short… that you are just not ready to quickly…, my body could just not take it. I had all kinds of negative effects from withdrawing, all kinds of symptoms I got." (woman, 50-59, partially discontinued)
II. Current experience with antidepressants		
Effectiveness	ADM does not help (anymore) *"… the idea that those things are not helping me anyway. I thought well, I am taking poison, and it doesn't really help." (man, 60-69, fully discontinued)*	ADM (still) works for me *"… if you are down and out again, then you actually already know it calls for another pill again, so to speak." (man, 50-59, not discontinued)*
Side effects	Side effects when using ADM *"Because I feel that my memory has gotten really worse. And when I was still fully on medication I noticed that my hands were just trembling a lot, and well.. I regarded that as a very bad sign (..) so I thought, I have to get rid of that." (woman, 50-59, partially discontinued)*	N/A
Withdrawal effects	N/A	Withdrawal effects *"I was using Citalopram and I believe I had to taper within 2 weeks, but I was suffering quite a lot from withdrawal symptoms, so therefore, after consultation, tapered somewhat more slowly." (woman, 20-29, fully discontinued)*
Tapering schedule	Individual, step by step *"And then it was advised to taper within 6 months, I discussed that with my doctor and he was not very keen on that and I thought I do not want to fall back again as I had done before. So for sure I am not going to taper as fast as the six months they suggested." (woman, 50-59, partially discontinued)*	Too fast and/or steps too big *"… so I have got something of a bit more tailoring to the person rather than just following the rules from the books" (man, 40-49, not discontinued)*

III. Life circumstances		
Psychosocial conditions	Relatively quiet period *"Just a quiet period so I thought I could put it to the test." (man, 60-69, fully discontinued)*	Social stressors *"I had just divorced, and I was sort of messing around with relationships and that was all quite turbulent. And then I easily got into, well, that I was really going into panic, and then quickly grabbed those pills again"(man, 50-59, fully discontinued, describing previous experience)*
Physical problems	N/A	Health problems *"I got a hernia when I was halfway through the MBCT course, therefore I wasn't able to finish the training and so I also didn't start tapering the medication" (woman, 60-69, not discontinued)*
IV. Clinical support		
Professional guidance	Availability and accessibility of clinician support *"And when there are signs that it doesn't go well, and there were, I just got a lot of support to really, yes, to keep it under control. And to just really stay with it." (woman, 20-29, completed)*	Negative view of discontinuation by attending clinician *"He [the psychiatrist] said: "I would not do it with your history and family matters". But I wanted to taper (..) and so I did." (woman, 50-59, partially discontinued)*
Empowerment (self-control)	Sharing ideas about type of support *"Time and listening to what people try to say. And not just*	Feeling forced *"The pressure to participate in the part of withdrawing medication, I*

	suddenly stopping everything, like it's always like this. Taking it seriously. (…) And I got offered a different kind of therapy." (woman, 50-59, partially discontinued) Freedom of choice *"I did feel a little tense before we started withdrawing. And, well, at a given moment you did have the guarantee that you if it really went wrong, you could always get back." (man, 60-69, fully discontinued)*	*actually found too high." (woman, 60-69, not discontinued)*
V. Mindfulness practice		
Group context	Peer support *"Never before I had participated in group therapy and to hear from others how they handle tapering and experience the same kind of problems, that gave me some understanding. I liked that. .." (woman, 50-59, partially discontinued)*	Negative opinion from fellow patients (in MBCT group) who did not taper *"So others were very fearful about it, those who were not in the group who were allowed or made to discontinue. They said, I would be careful with this, and so on. Yes, and I had the same idea." (man, 60-69, fully discontinued).*
Mindfulness skills	Cope with distress *"Then somebody said "why don't you restart medication for a while?" and another said: "go get some antidepressant medication". And then I said, no that is not useful. I know the cause of my problem and I know why I am feeling tense now [financial worries]. Maybe I am a little unhappy now but I am not depressed, I just feel it." (man, 60-69, fully discontinued)* Relapse prevention	

"it [relapse prevention plan] contained elements that made me feel better. Like doing nice things with other people and make sure you keep structure in your day."(woman, 20-29, fully discontinued)

Reporting checklist for qualitative study.

Based on the SRQR guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SRQR reporting guidelines, and cite them as:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. Acad Med. 2014;89(9):1245-1251.

		Reporting Item	Page Number
	#1	Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g. ethnography, grounded theory) or data collection methods (e.g. interview, focus group) is recommended	**1**
	#2	Summary of the key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results and conclusions	**2-3**
Problem formulation	#3	Description and signifcance of the problem / phenomenon studied: review of relevant theory and empirical work; problem statement	**5**
Purpose or research question	#4	Purpose of the study and specific objectives or questions	**5**
Qualitative approach and research paradigm	#5	Qualitative approach (e.g. ethnography, grounded theory, case study, phenomenolgy, narrative research) and	**7**

		guiding theory if appropriate; identifying the research paradigm (e.g. postpositivist, constructivist / interpretivist) is also recommended; rationale. The rationale should briefly discuss the justification for choosing that theory, approach, method or technique rather than other options available; the assumptions and limitations implicit in those choices and how those choices influence study conclusions and transferability. As appropriate the rationale for several items might be discussed together.	
Researcher characteristics and reflexivity	#6	Researchers' characteristics that may influence the research, including personal attributes, qualifications / experience, relationship with participants, assumptions and / or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results and / or transferability	**7**
Context	#7	Setting / site and salient contextual factors; rationale	**6**
Sampling strategy	#8	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g. sampling saturation); rationale	**7**
Ethical issues pertaining to human subjects	#9	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	**6**
Data collection methods	#10	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources / methods, and modification of procedures in response to evolving study findings; rationale	**6-7**
Data collection instruments and technologies	#11	Description of instruments (e.g. interview guides, questionnaires) and devices (e.g. audio recorders) used for data collection; if / how the instruments(s) changed over the course of the study	**7**
Units of study	#12	Number and relevant characteristics of participants, documents, or events included in the study; level of	**12**

		participation (could be reported in results)	
Data processing	#13	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymisation / deidentification of excerpts	**9**
6Data analysis	#14	Process by which inferences, themes, etc. were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale	**9**
Techniques to enhance trustworthiness	#15	Techniques to enhance trustworthiness and credibility of data analysis (e.g. member checking, audit trail, triangulation); rationale	**9, 15,16**
Syntheses and interpretation	#16	Main findings (e.g. interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	**12-16**
Links to empirical data	#17	Evidence (e.g. quotes, field notes, text excerpts, photographs) to substantiate analytic findings	**supplement 1**
Intergration with prior work, implications, transferability and contribution(s) to the field	#18	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application / generalizability; identification of unique contributions(s) to scholarship in a discipline or field	**17**
Limitations	#19	Trustworthiness and limitations of findings	**18**
Conflicts of interest	#20	Potential sources of influence of perceived influence on study conduct and conclusions; how these were managed	**9, 18**
Funding	#21	Sources of funding and other support; role of funders in data collection, interpretation and reporting	**20**