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Research paper

Recovery from recurrent depression: Randomized controlled trial of the efficacy of mindfulness-based compassionate living compared with treatment-as-usual on depressive symptoms and its consolidation at longer term follow-up

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A B S T R A C T

Introduction: Mindfulness-Based Cognitive Therapy (MBCT) has been shown to reduce depressive symptoms in patients with recurrent or chronic depression. However, sequential, follow-up interventions are needed to further improve outcome for this group of patients. One possibility is to cultivate mechanisms thought to support recovery from depression, such as (self-)compassion. The current study examined the efficacy of mindfulness-based compassionate living (MBCL) in recurrently depressed patients who previously received MBCT, and consolidation effects of MBCL at follow-up.

Methods: Part one is a randomized controlled trial (RCT) comparing MBCL in addition to treatment as usual (TAU) with TAU alone. The primary outcome measure was severity of depressive symptoms. Possible mediators and moderators of treatment outcome were examined. Part two is an uncontrolled study of both intervention- and control group on the consolidation of treatment effect of MBCL over the course of a 6-months follow-up period.

Results: Patients were recruited between July 2013 and December 2014 ($N = 122$). MBCL participants ($n = 61$) showed significant improvements in depressive symptoms (Cohen's $d = 0.35$), compared to those who only received TAU ($n = 61$). The results at 6-months follow-up showed a continued improvement of depressive symptoms.

Limitations: As MBCL was not compared with an active control condition, we have little information about the possible effectiveness of non-specific factors.

Conclusion: MBCL appears to be effective in reducing depressive symptoms in a population suffering from severe, prolonged, recurrent depressive symptoms. To optimise the (sequential) treatment trajectory, replication of the study in a prospective sequential trial is needed.

Registered at ClinicalTrials.gov: NCT02059200

1. Introduction[1]

Major depressive disorder (MDD) is characterised by persistent symptoms and high relapse rates (Mueller et al., 1999). Mindfulness-based cognitive therapy (MBCT) has been demonstrated to reduce the risk of a relapse/recurrence in patients with recurrent depression in remission in a 60-week follow-up period by 31% (Kuyken et al., 2016). Given their high psychological, social and economic burden as well as their predictive value in terms of relapse, the treatment of current depressive symptoms is also very important (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). A growing number of studies indicate that MBCT may also be effective in decreasing depressive symptoms in patients with current depression (Strauss, Cavanagh, Oliver, & Pettman, 2014). However, residual symptoms seem to remain considerable even after MBCT (Piet and Hougaard, 2011), leaving substantial room for further improvement.

Reduction of rumination is one of the most established working mechanisms of MBCT. A meta-analysis by Van der Velden et al. ($N = 23$; Van der Velden et al., 2015) reported that alterations in rumination, worry and meta-awareness were associated with, predicted or mediated MBCT outcome. However, not only reduction in rumination and increase in mindfulness skills were demonstrated to be mediators of treatment outcome, also compassion. Since one of the possible underlying mechanisms for the chronic and recurrent nature of MDD is low self-esteem or self-denigration (Gilbert & Procter, 2006), the finding that compassion mediates MBCT's treatment effect is interesting. Being able to adopt a caring attitude towards the self might be a skill that could help reduce the undermining mechanisms of self-

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[1] MBCT: Mindfulness-based Cognitive Therapy; MBCL: Mindfulness-based Compassionate Living; RCT: Randomized controlled trial; TAU: Treatment-as-usual.

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criticism and hence reduce the vulnerability to recurrence or persistence of depressive symptoms. As self-compassion is taught mostly implicitly in MBCT (Segal et al., 2012), the explicit cultivating of self-compassion may pay a complementary contribution to reduction of rumination and increase in mindfulness skills in the prevention of depressive relapse or recurrence, or reduction of depressive symptoms.

To this end, Van den Brink and Koster (2015) developed mindfulness-based compassionate living (MBCL), a training to cultivate compassion in patients who previously participated in MBCT. The advantage of offering MBCL as a follow-up to MBCT is that participants have already laid the foundation of non-judgmental, present-moment awareness before exposing themselves more actively to difficult, painful experiences with a (self)compassionate attitude. A first pilot study on MBCL in patients with a variety of psychiatric disorders who previously followed mindfulness-based stress reduction (MBSR) or MBCT showed a reduction in depressive symptoms and increases in both mindfulness and self-compassion skills (Bartels-Velthuis et al., 2016). A pilot study of our own group showed that MBCL appeared to be feasible and acceptable in 17 patients with recurrent depression who previously followed MBCT, and demonstrated some preliminary improvements of depression and self-compassion (Schuling et al., 2017). The pilot was primarily focused on facilitators and barriers of MBCL, which helped us tailor it to our population by using a qualitative co-creation design.

Offering MBCL after MBCT could be conceptualised as a sequential treatment. Sequential treatment designs are more commonly known in both pharmacological treatments of depression (Popova et al., 2019) and the combination of pharmacotherapy and psychological treatment (Cuijpers et al., 2020). In contrast, MBCT and MBCL are both psychological treatments.

Targeting depressive symptoms with a double or sequential treatment has particular advantages: it allows randomization of patients to treatment alternatives according to stages of development of their illness and not simply to disease classification. The model is thus more in line with the chronicity of mood disorders compared to the standard randomized controlled trial, which is based on the acute disease model (Fava and Tomba, 2010). In addition, sequential treatment seems to be more effective than single treatments (Cuijpers et al., 2020). Given the percentage of people that doesn't improve with a primary treatment, using additional treatment in a sequence seems a fruitful approach. One option is to follow a pragmatic approach, offering the second treatment to a population that has already followed the first (Daly et al., 2018). Ideally however, the efficacy is tackled by a prospective study offering both treatments in sequence to a population that has received neither before (Popova et al., 2019). As little is known about MBCL efficacy in patients with recurrent depression, we decided to use the pragmatic approach by offering MBCL to a population that had previously followed MBCT.

In this paper, two studies are reported. Study 1 is an RCT comparing MBCL and TAU in their efficacy to further reduce depressive symptoms in patients with recurrent depression who previously participated in MBCT. As secondary outcomes in the RCT we assess current depression status, rumination, self-compassion, mindfulness and quality of life. We also examine possible mediators and moderators of treatment outcome. Study 2 is an uncontrolled follow-up study of both the original MBCL condition and the patients who were offered MBCL after completion of TAU to investigate the consolidation of treatment outcome using the same outcome measures.

2. Method - STUDY I

2.1. Study design

The first study was a parallel-group RCT, in which patients who had previously participated in MBCT were randomized to MBCL combined with TAU or TAU alone. Assessments took place at baseline and after treatment (four months after baseline). The study was carried out at the Radboudumc Centre for Mindfulness in the Netherlands, from July 2013 to April 2015, with follow-up assessments continuing until November 2015. The protocol was approved by the ethical review board CMO Arnhem-Nijmegen (2013/220) and published (Schuling et al., 2016). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

2.2. Participants

The study population consisted of adults (⩾18 years of age) who had been diagnosed with recurrent depressive disorder at the Radboudumc and had previously participated in an MBCT course at the same institute (⩾4 sessions, at least one year prior to this study). Patients were invited to participate by letter. If interested, they were invited for a research interview, during which the in- and exclusion criteria were assessed (cf. trial design and protocol paper; Schuling et al., 2016). In case of eligibility, written informed consent was obtained, after which relevant socio-demographic data were collected, including the Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998), and participants were randomized. Both intervention and control group completed a post-treatment at four months after baseline.

2.3. Randomization and masking

Randomization to the two conditions was performed on a 1:1 ratio using a website-based application, developed specifically for this study by an independent statistician. The randomization took place in blocks of four minimizing for the following variables: depression status (current depression/partial remission/full remission), age of onset (<21/ 21–30/ 31–38/ >39), number of episodes (1–2/ 3–4/ >5) and presence of childhood trauma in terms of physical or sexual abuse during childhood. Presence of trauma was operationalised as at least one item pertaining to physical or sexual abuse on the CTQ being answered positively. An example of such an item is: “During my childhood, someone wanted me to perform sexual acts or watch sexual acts.”

Participants were informed about the condition they had been assigned to by the first author, who also conducted the post-treatment and 6-months follow-up assessments for which she consequently was not blinded.

2.4. Interventions

2.4.1. MBCT (prior to RCT)

Prior to participating in MBCL, all participants had followed MBCT, which was originally developed as a relapse prevention program for remitted patients (Segal et al., 2012). MBCT is an adaptation of MBSR, developed in the late 1970s for patients with chronic pain or medically unexplained symptoms (Kabat-Zinn, 1990). A frequently used definition of ‘mindfulness’ is “paying attention in a particular way: on purpose, in the present moment, and non-judgmentally” Kabat-Zinn, 1994 (p.4). MBCT is a group-based intervention consisting of eight 2.5-hour sessions and one ‘day of silence’ in the second half of the training (Segal, 2012). Additionally, participants are encouraged to practice at home for 30 to 45 minutes a day. The practices consist of formal and informal techniques such as the ‘body scan’, sitting meditation, gentle movement based on hatha yoga, and the ‘three-minute breathing space’. The mindfulness meditation techniques are combined with elements of Cognitive Behavioural Therapy (CBT). In contrast to CBT, MBCT aims to cultivate decentering, i.e. experiencing thoughts as activity in the mind, by focusing on the process of thinking rather than the content of negative thoughts. Implicitly, a friendly attitude towards this process is encouraged. Group inquiry, which is part of the programme, is also geared towards this.

2.4.2. MBCL

Based on the pilot study, MBCL was delivered as a group-based

intervention consisting of eight 2.5-hour sessions once every two weeks (Schuling et al., 2017). The format of the programme was similar to MBCT, containing a mixture of mindfulness practice, group inquiry and didactic and interactive teaching. Patients were invited to practice at home for about 30 minutes on a daily basis, supported by CDs. A more elaborate description of the intervention is provided in both our pilot study (Schuling et al., 2017) and published protocol (Schuling et al., 2016).

MBCL was delivered in groups of about 8-10 participants taught by one of two teachers. Both teachers met the Good Practice Guidelines for teaching mindfulness-based courses by the UK Network for Mindfulness-Based Teacher Training Organizations (Crane et al., 2013) and had been trained to teach MBCL by its developers Koster and Van den Brink. Treatment integrity and therapist competence was assessed by two experienced, independent raters as competent, based on two randomly selected videotapes of each teacher using the mindfulness-based intervention teacher assessment criteria (MBI:TAC) (Crane et al., 2013).

2.4.3. TAU

In our study, TAU consisted of all medical and psychological treatments received between baseline and post-treatment (four months), which were recorded using the TIC-P (Hakkaart-van Roijen et al., 2002).

2.4.4. Outcome measures

All measures are described extensively in Schuling et al. (2016). The primary outcome measure was severity of depressive symptoms, measured by the Beck Depression Inventory-II (BDI-II-NL) (Van der Does, 2002). It contains 21 items, scored on a 0-3 scale and its internal consistency was 0.90. Depression status in terms of current depression, partial or full remission was assessed with the Structured Clinical Interview for DSM-IV disorders (SCID), part 1 (First et al., 1996), by a trained assessor. All interviews were audio taped and a random sample of $N = 30$ interviews was second-rated by an independent and blind assessor to assess inter-rater reliability. The agreement between first and second ratings was found to be moderate (kappa (κ) = 0.60, 95% CI = 0.45 to 0.76, $p = .000$) McHugh, 2012, the percentage of agreement was 87%. Rumination was assessed with the brooding subscale of the Ruminative Response Scale (Raes, Hermans, & Eelen, 2003). We selected the brooding subscale because over time, brooding has been related to higher levels of depression, whereas the reflection subscale has been linked to lower levels of depression (Treynor et al., 2003). The internal consistency was 0.63. Self-compassion was measured using the Self-Compassion Scale (Raes, Pommier, Neff, & Van Gucht, 2011). The internal consistency was 0.93. Mindfulness skills were measured using the Five Facet Mindfulness Questionnaire (FFMQ-NL) (Bohlmeijer, Peter, Fledderus, Veehof, & Baer, 2011). The internal consistency was 0.91. Quality of life was measured using the 26-item self-report WHO-QoL short version (WHO-QoL-bref) of the WHO-QoL (The Whoqol Group, 1998). Items are scored on a 5-point scale. The internal consistency was 0.92.

As described in our protocol (Schuling et al., 2016), all measures (including the SCID) were assessed at baseline, at post-treatment four months after baseline, and at follow-up six months after completion of the treatment.

2.5. Statistical analysis

A total of 104 participants (52 per group) was needed to demonstrate a difference of minus four on the Beck Depression Inventory, with a power of 0.80 and alpha of 0.05 (Schuling et al., 2016). Taking account of possible dropout, we aimed to recruit N = 120 patients for the study.

2.6. Analysis of the efficacy of MBCL

We report intention-to-treat (ITT) analyses based on complete cases in terms of assessments. In line with the protocol, we used ANCOVA analyses to compare post-treatment scores on all measures between the two groups, controlling for baseline levels. We also entered the minimisation criteria used for randomization, i.e. depression status, age of onset, number of previous episodes and presence of childhood trauma, as covariates. Additionally, a Cohen's *d* type effect size was calculated for each measure, by dividing the (adjusted) mean difference at post-treatment by the pooled standard deviation at pre-treatment for each measure.

We used multiple imputation modelling as a sensitivity analysis, creating ten imputed datasets based on the minimisation criteria, sex, age and the primary and secondary outcome measures. We then ran an ANCOVA on the imputed datasets using the minimisation criteria as covariates, analogous to our main analysis.

2.6.1. Mediation analysis

In line with the protocol, we conducted the mediation analyses following the recommendations of Preacher and Hayes (2008) for multiple mediation models. In all mediation analyses, severity of depressive symptoms at post-treatment was controlled for baseline levels. Standardised residualized change scores for all potential mediators (rumination, self-compassion and mindfulness) were calculated (MacKinnon, 2008). We first assessed the indirect effect of all potential mediators using a univariate model and, if shown to be a mediating factor, they were entered into a multivariate model in order to assess their possibly independent contribution. A nonparametric bootstrapping method was used to assess the indirect effect based on 5000 bootstrapped samples using bias corrected and accelerated 95% confidence intervals (BCa CI) as provided by Hayes (2017) [SPSS PROCESS macro version 3.3].

2.6.2. Moderation analysis

All moderation analyses were performed on severity of depressive symptoms at post-treatment, using residualized change scores. Moderation analyses were performed using univariate analyses of variance (ANOVA) for a) age, b) gender, c) diagnostic status for MDD (current depression/full remission), d) number of previous episodes (1-2/ 3-4/ 5+), e) age of onset (0-20/ 21-30/ 31-38/ 39+) and f) presence of childhood trauma (considered present when at least one item of the CTQ pertaining to physical or sexual abuse was answered positively). The analyses were performed for each moderator separately, using condition, the moderator and the interaction term condition x moderator.

3. Method - STUDY II

3.1. Design

The second study is an uncontrolled follow-up study of the combined sample of the patients in the initial MBCL group and those who received MBCL after having completed the TAU period of four months in the control condition. In this study, we used the end-of-control assessment as baseline for the participants who had been randomized to TAU only. Further assessments for this study took place after treatment and at six months after completion of treatment. All RCT outcome measures were used in this study as well.

3.2. Statistical analysis

3.2.1. Consolidation of treatment outcome at 6-months follow-up

Linear mixed effect models were used to analyse consolidation of treatment effects on the primary and secondary outcome measures in the combined ITT sample. We also report the within group effect size

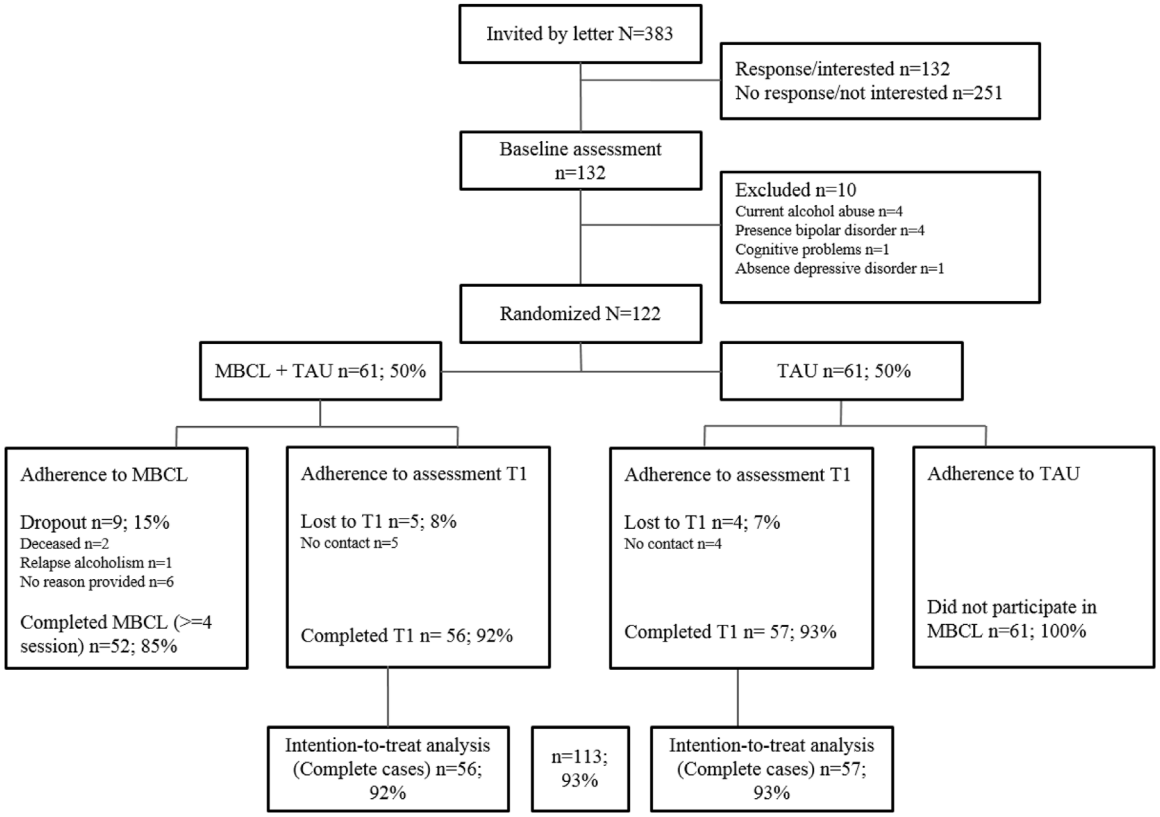

Fig. 1a. RCT CONSORT diagram: Flow of participants from screening to analysis, comparing MBCL + TAU to TAU alone. MBCL: Mindfulness based compassionate living; TAU, Treatment-as-usual; T1, end-of-treatment / end-of-control assessment.

for both the pre- to post-treatment and the 6-months follow-up period. Separate models were run for each of the outcomes, in which the particular outcome measure was used as dependent variable. Time (post-treatment/follow-up) was used as within subject factor, and the baseline assessment was added as covariate, to control for baseline severity. We used the post-TAU scores of the TAU alone group as baseline assessment for the follow-up study, as these were closer in time to the start of MBCL. There were no differences between pre-and post-TAU scores in the TAU alone group. A random intercept for participants was added to account for dependency in the data due to repeated assessments. We used a restricted maximum likelihood estimation, as this estimation methods deal effectively with missing data (Newman, 2014) and we used a diagonal covariance structure.

4. Results - STUDY I

4.1. Participant flow and characteristics

A total number of 122 patients were included in the study (MBCL + TAU: $n = 61$, TAU: $n = 61$; cf. Fig. 1a for a detailed description of the patient flow). The average time elapsed since participating in MBCT was 4,1 years for the MBCL group vs. 4,5 for the TAU group (range 1–7 years). In total, 11 groups were delivered, containing an average of 5,5 MBCL + TAU participants per group. The first group only contained MBCL + TAU participants, after this, the groups were mixed between MBCL + TAU and TAU only participants. Therefore TAU only participants received MBCL in ten groups, averaging 6.1 participants per group. Average attendance for the MBCL group was 6,1 sessions (SD: 2,4). Participant demographic and clinical characteristics for both the RCT and the combined follow-up sample are detailed in Table 1.

No differences in percentage of patients using health care services during the intervention period were observed between the two conditions (see Table 2). However, with the exception of their general practitioner, TAU participants paid significantly more visits to all health care providers than MBCL participants.

4.2. Efficacy of MBCL

The ITT analysis based on complete cases showed that the MBCL group had less depressive symptoms after MBCL than the TAU group ($d = 0.35$; $p = .034$). The results correspond with a number-needed-to-treat of 5. As we did not find any baseline differences between those who completed the post-treatment assessments and those who did not, the sensitivity analyses were conducted with the assumption that missing data (7.4%) were missing at random (MAR). Multiple imputation analysis showed a significant reduction in depressive symptoms in seven of the ten imputed datasets.

In the MBCL condition, 36,7% of the MBCL participants was depressed at baseline ($n = 60$) and 24,5% at post-treatment ($n = 53$). In the TAU group, 29,3% was depressed at baseline ($n = 58$) and 40,7% at post-treatment ($n = 54$). These percentages did not differ significantly between the groups ($p = .074$).

Table 3 shows all other secondary outcomes at post-treatment. We found a significant reduction in rumination in the MBCL compared with the TAU group ($d = 0.38$, $p = .011$). In addition, MBCL was associated with significant improvements in self-compassion ($d = 0.41$; $p = .002$), mindfulness skills ($d = 0.39$; $p = .004$), and quality of life ($d = 0.63$; $p = .000$).

4.3. Mediation of MBCL's effect

For the reduction in depressive symptoms, the univariate analyses showed a mediating role for rumination, self-compassion and mindfulness skills. In the multivariate model, only self-compassion remained a significant mediator (cf. Fig. 2).

Table 1
Baseline demographic and clinical characteristics of participants[a] in the RCT sample (MBCL added to TAU and TAU only) and the FU sample (the joint follow-up sample).

Variable	MBCL (N = 61)	TAU (N = 61)	FU (N = 122)
Female	47 (77%)	44 (72.1%)	91 (74.6%)
Age (years) *mean* ± *SD*	55.9 ± 8.7	55.3 ± 12.4	55.6 ± 10.6
Educational level			
Low	3 (4.9%)	5 (8.2%)	8 (6.6%)
Middle	48 (78.7%)	38 (62.0%)	86 (70.5%)
High	9 (14.8%)	14 (23.0%)	23 (18.9%)
Marital status			
Married/cohabiting	38 (62.3%)	38 (62.3%)	76 (62.3)
Divorced/widowed	9 (14.8%)	6 (9.8%)	15 (12.3)
Single	13 (21.3%)	13 (21.3%)	26 (21.3%)
Employed	33 (54.1%)	30 (49.2%)	63 (51.6%)
Current ADM use	27.0 (44.3%)	30.0 (49.2%)	57 (46.7%)
Three or more previous episodes[b]	53.0 (86.9%)	53.0 (86.9%)	106 (86.0%)
Age at MDD onset[b] (years) *mean* ± *SD*	23.8 ± 11.2	26.3 ± 13.0	25.0 ± 12.2
Presence of childhood trauma[c]	27.0 (44.3%)	26.0 (42.6%)	53 (43.4%)
Time since MBCT[d] (years) *mean* ± *SD*	4.1 ± 1.9	4.5 ± 1.8	4.3 ± 1.9
Depressive symptoms (BDI-II) *mean* ± *SD*	17.8 ± 10.4	15.8 ± 11.2	16.8 ± 10.8
Current depression (SCID-I)	20.0 (32.8%)	17.0 (27.9%)	37 (30.3%)

ADM: Anti-depressant medication; BDI-II: Beck Depression Inventory; FFMQ: Five Facet Mindfulness Questionnaire; FU: follow-up; MBCT: Mindfulness-Based Cognitive Therapy; MDD: Major depressive disorder; RCT: randomised controlled trial; RRS-brood: Ruminative Response Scale, subscale *brooding*; SCID-I: Structured Clinical Interview for DSM-IV Axis I disorders part I; SCS: Self-Compassion Scale; SD: Standard deviation; TAU: treatment-as-usual; WHOQOL-Bref: World Health Organization Quality of Life- abbreviated version.

[a] Other nationalities: German (3), Belgian (3), French (2), Czech (1). All were fluent in Dutch.

[b] Based on self-report.

[c] Presence of physical or sexual abuse as measured by the physical and sexual abuse subscales of the childhood trauma questionnaire (Bernstein & Fink, 1998).

[d] Five participants had attended MBCT twice in the past.

4.4. Moderation of MBCL's effect

Only age and age of onset appeared to be moderators of treatment outcome, i.e. those who were younger or had an earlier age of onset benefited more from MBCL (Cohen's d = 0.56, p = .004 and Cohen's d = 0.40, p = .040 respectively). Presence of childhood trauma appeared not to be a moderator of treatment outcome.

4.5. Adverse events

Two patients randomized to the intervention group unfortunately died by suicide. Both were randomized into the MBCL condition. As one suicide occurred before the start of MBCL, and the other after one session only, the medical ethical committee of the region Arnhem-Nijmegen considered the events to be unrelated to the patients' participation in the study.

5. Results - STUDY II

5.1. Participant flow and characteristics

From the 61 patients assigned to the control group, n = 57 (93%) accepted the invitation to participate in the MBCL after completion of the TAU period. So, the combined sample of both the original MBCL group and the patients who received MBCL after the TAU group was N = 119. Average attendance overall was 6,2 sessions (SD: 2,4). The flow of participants from RCT to the 6-months follow-up is presented in Fig. 1b. The baseline characteristics of the combined group can be found in Table 1.

5.2. Change of primary and secondary outcome measures

From start-of-treatment to end-of-treatment we found no reduction in depressive symptoms in the combined sample (within-groups effect size d = 0.41, p = .064). A significant difference in diagnostic status for MDD was found in the combined sample: 33,1% was depressed at baseline (n = 118) and 25,7% at post-treatment (n = 113) (p = .002). We observed improvements from pre- to post-treatment in all other outcomes except quality of life. The results are presented in Table 4.

5.3. Consolidation of treatment outcome at 6-months follow-up

In the combined sample, there was a significant decrease in the primary outcome, severity of depressive symptoms, from post-treatment to follow-up ($p \leq .001$, cf. Table 4). Within group effect size (Cohen's d) for the combined population from post-treatment to follow-up was 0.67 and from pre-treatment to follow-up 1.07. In diagnostic status for MDD in the combined sample we found 36,0% was depressed at follow-up (n = 89), this differed significantly from the post-treatment results (p = .044). We observed improvements from post-treatment to follow-up in all other outcomes except rumination (cf. Table 4).

Table 2
*Utilisation of usual care, other than trial intervention, in the Mindfulness-Based Compassionate Living and Treatment As Usual group from baseline measurement to post-treatment.

Type of care	MBCL N = 21[a] (35%) Users; N (%)	Mean nr of visits[b] (SD)	TAU N = 30[a] (48%) Users; N (%)	Mean nr of visits[b] (SD)	p^{users}	p^{visits}
General practitioner	15 (71%)	1.4 (0.9)	23 (77%)	1.9 (1.0)	.458	.710
Psychiatrist	3 (14%)	0.7 (1.7)	8 (27%)	1.6 (2.7)	.241	.001
Psychologist/psychotherapist	3 (14%)	1.1 (2.8)	7 (23%)	3.0 (5.5)	.334	.000
Other[c]	14 (67%)	5.6 (4.0)	19 (63%)	6.1 (4.7)	.523	.045
Hospitalisation[d]	1 (5%)	n.a.	0 (0%)	n.a.	.412	n.a.
General outpatient care	7 (33%)	0.9 (1.2)	16 (53%)	1.0 (0.9)	.130	.003
(m)ADM	11 (52%)	n.a.	16 (53%)	n.a.	.586	n.a.

* This table serves only to compare TAU for both arms of the study, therefore information on MBCL is excluded.

[a] Due to a technical-procedural error not all TAU was assessed during the intervention period. Data were available for 21 (35%) of participants in MBCL and for 30 (48%) in TAU.

[b] Calculated for the group of users.

[c] Including physiotherapist, acupuncturist etc.

[d] Dep. of gynaecology

Table 3
Post-treatment levels of depressive symptoms, quality of life, rumination, self-compassion skills and mindfulness skills after Mindfulness-based compassionate living (MBCL) or Treatment-as-usual(TAU), controlling for baseline levels of depression.

Primary measure	Mean (SD)				Group difference (95% CI)[a]	p	d
	MBCL (n = 56)		TAU (n = 57)				
	Pre	Post	Pre	Post			
BDI-II	17.79 (10.42)	13.77 (10.63)	15.80 (11.18)	15.68 (11.64)	−3.75 (−7.21 to −0.29)	.034	0.35
Secondary measures							
RRS-Brood	11.61 (3.05)	10.70 (3.01)	11.90 (2.95)	11.93 (2.70)	−1.15 (−2.003 to −0.27)	.011	0.38
SCS	21.31 (6.18)	24.47 (5.84)	20.52 (5.70)	21.83 (5.67)	2.43 (0.93 to 3.93)	.002	0.41
FFMQ	122.52 (16.99)	128.31 (20.0)	119.97 (19.22)	120.65 (20.86)	7.12 (2.30 to 11.95)	.004	0.39
QoL-bref	87.12 (14.20)	93.17 (14.57)	90.05 (14.71)	87.11 (15.94)	9.05 (4.86 to 13.23)	.000	0.63

BDI-II: Beck Depression Inventory; RRS: Ruminative response Scale; SCS: Self-Compassion Scale; FFMQ: Five Facet Mindfulness Questionnaire; WHOQOL-Bref: World Health Organization Quality of Life- abbreviated version; PP: per protocol.
[a] Corrected for baseline values.

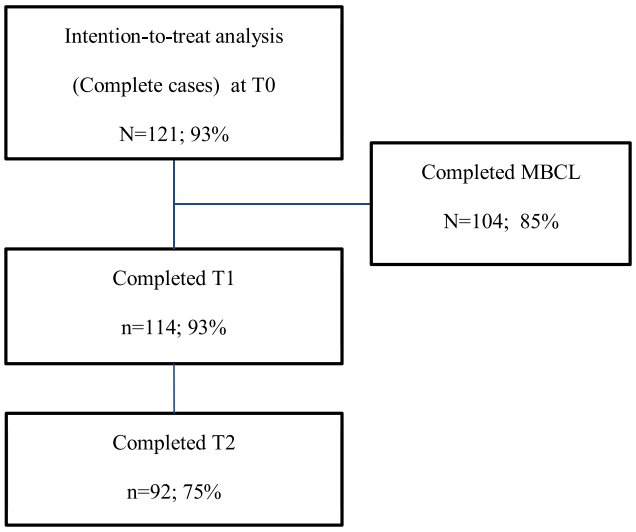

Fig. 1b. 6-months follow-up CONSORT diagram: MBCL, Mindfulness based compassionate living; TAU, Treatment-as-usual; T1, end-of-treatment / end-of-control assessment; T2, 6-months follow-up assessment.

6. Discussion

6.1. Summary and comparison with the literature

The present study is the first trial examining the efficacy of MBCL in patients with recurrent depression, who previously followed MBCT. Our findings indicate that MBCL, offered as a sequential intervention to MBCT, results in a significant reduction of depressive symptoms at post-treatment (d = 0.34), corresponding with a number-to-treat of five. Furthermore, we found a reduction of rumination and improvements in self-compassion, mindfulness skills and quality of life in MBCL versus TAU. In the follow-up study containing the combined population, we found a comparable effect size to the RCT study from pre- to post-treatment (Cohen's d of 0.41), though the difference was not significant. For the pre-treatment to follow-up period we found a large effect size: 1.07.

As MBCT is also known to reduce depressive symptoms and rumination, and increase mindfulness skills and self-compassion (Van Aalderen et al., 2012), the improvements observed in the MBCL group are noteworthy. In a group of patients with relatively severe symptoms, the large effect size for the improvement of quality of life is particularly encouraging. This improvement was larger than in a similar population treated with MBCT (Van Aalderen, Donders et al., 2012), using the same instrument. It is possible that the more active and explicit compassionate approach to difficult experiences in MBCL, compared with the more implicit focus on compassion in MBCT, is responsible for this difference.

As previously demonstrated for MBCT (Van der Velden et al., 2015), self-compassion appeared to be a mediator of treatment outcome of MBCL, lending support to self-compassion being the hypothesized working mechanism of MBCL. It is noteworthy that no mediation for rumination was found in MBCL, as it has been consistently found to be a mediator of MBCT (Van Aalderen, 2015). This suggests the working mechanisms of MBCL might be different and possibly complementary to those of MBCT. Furthermore, the program appeared most effective for those who were younger and/or had an earlier age of onset. This is partly in accordance with previous studies which have shown treatment outcome of MBCT to be moderated by variables related to an underlying vulnerability to depressive symptoms, such as childhood trauma, baseline severity of depressive symptoms, number of previous episodes

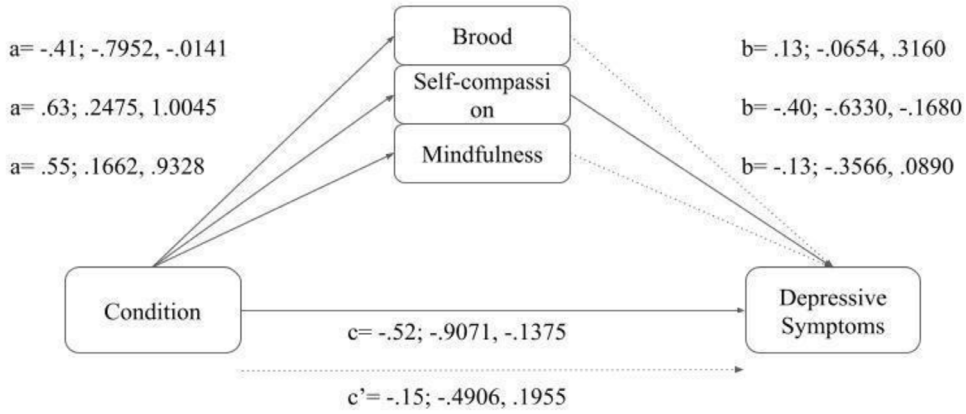

Fig. 2. Multivariate mediation of treatment outcome in depressive symptoms.

Table 4
Means and standard deviations of uncontrolled follow-up data, and results of linear mixed effect models regarding consolidation effect (N = 119).

	Pre-MBCL[a] M ± SD	Post-MBCL M ± SD	Follow-up M ± SD	Pre- to post-MBCL analyses Cohen's d[c]	p	Consolidation analyses[b] Cohen's d[c]	p
Depressive symptoms	16.76 ± 10.98	14.75 ± 11.09	11.39 ± 11.39	0.42	.064	0.67	<.001
Brooding	11.78 ± 2.87	11.35 ± 2.91	10.73 ± 2.96	0.30	.046	0.47	.137
Self-compassion	21.54 ± 5.90	23.09 ± 5.87	25.10 ± 6.42	0.82	.000	0.74	<.001
Mindfulness	121.54 ± 18.84	124.31 ± 20.65	131.76 ± 21.70	0.35	.026	0.79	<.001
Quality of life	87.18 ± 14.91	90.02 ± 15.35	93.51 ± 17.30	0.22	.450	0.48	.011

[a] These baseline values reflect the baseline score for the MBCL group and the post-TAU score (pre-MBCL) for the TAU group.
[b] Linear mixed effect models to test the difference between post-MBCL and six-month follow-up, controlled for the baseline level before MBCL.
[c] Within groups.

and age of onset (Williams et al., 2014). However, in contrast with previous studies of MBCT (Kuyken et al., 2016), presence of childhood trauma did not moderate treatment outcome of MBCL. Rumination was not found to be a moderator of treatment outcome either, whereas in a sample of chronically depressed, treatment-resistant patients following MBCT, it was (Cladder-Micus et al., 2018).

In the RCT part of the study, the comparison with the control group takes account of regression towards the mean. For the uncontrolled follow-up study, this might be a problem. But given the reduction of depressive symptoms during the treatment phase of the study, one would expect this to mitigate in the follow-up phase. In contrast, we actually observed a further reduction, which supports the findings of study I (RCT). As residual symptoms are an important predictor of depressive relapse and recurrence, this finding supports the potential clinical relevance of MBCL, and its possible influence on relapse rates. Furthermore, we found small improvements in rumination, self-compassion and mindfulness skills and a moderate increase in quality of life and in MBCL versus TAU. This observation of consolidation or further improvement over the course of follow-up rather than attenuation of treatment effect has in fact been demonstrated in earlier studies of MBIs for both patients with ADHD and cancer patients (Cillessen et al., 2018, Janssen et al., 2019), as well as patients suffering from recurrent depressive symptoms (Van Aalderen, 2015). This may be due to the experiential rather than cognitive nature of both MBCT and MBCL, including regular practice, therefore having the potential to structurally change habitual patterns. This change may result in continued improvements over time.

6.2. Strengths and limitations

The main strengths of the current study are its adequate sample size, randomized controlled design and innovative nature, as this is one of the first studies investigating the efficacy of MBCL for patients with recurrent depression who previously followed MBCT. Though our approach to the sequential treatment design was pragmatic, the sequencing of MBCT and MBCL is another strength, given that such designs better fit the chronic, recurrent nature of depression (Cuijpers et al., 2020). Especially for patients suffering from relatively severe symptoms, as in our sample, a sequential approach might prove more efficacious. Furthermore, inclusion of participants went smoothly and we had low levels of attrition, signalling that MBCL is not only acceptable to this population but even seems to meet a tacit need. In addition, we were able to work with teachers with long-standing experience, who were trained by the MBCL-developers themselves. Testing mediation is also a strength of this study, as it tells us something about the specificity of the efficacy of MBCL, and the study explored possible moderating variables that may influence the reduction in depressive symptoms. Additionally, we looked at the consolidation of treatment effect in an uncontrolled sample including participants from both intervention and control group, who received MBCL after completing the TAU alone period.

The pragmatic nature of the sequential treatment design is also one of the limitations of this study: participation was offered to all former MBCT participants who met the in- and exclusion criteria, so we did not, for example, select participants who did not remit after MBCT. In addition, the time elapsed between MBCT and MBCL varied greatly. Consequently, we do not have any information about a possible selection bias of the participants in the study: we have little insight into the characteristics of those who responded versus those who did not. In the previous MBCT trial, BDI-II levels had dropped from 14.9 to 10.3 during MBCT (Van Aalderen, Donders et al., 2012). However, a 2011 systematic review showed that even after MBCT, room for improvement remains (Piet and Hougaard, 2011). So our population may have consisted of patients with remaining symptoms after MBCT, for whom MBCT might have been less effective. In addition, at the start of our current study, baseline levels of depression were even higher (BDI-II: 16,8), suggesting the study attracted patients in need of another treatment, who may have been interested in using MBCL to reconnect with the practices learned in MBCT.

Though our recruitment strategy, inviting MBCT participants with and without depression and using relatively few exclusion criteria, increases generalisability to the 'normal' clinical setting, a systematic, prospective sequential trial should be conducted, assigning patients to initial MBCT followed by MBCL or to initial MBCT only. This would help to gain more information about the proportion and characteristics of those patients who might benefit from additional MBCL in comparison with MBCT alone, and enable proper investigation of potential moderators.

It is also possible (part of) the effects of the trial might be due to a double dosage of treatments rather than to the effect of MBCL specifically. Additionally, we did not compare MBCL with an active control condition. Consequently, we have little information about the specificity of the treatment effect. To investigate both double dosage and specificity, one might need to compare MBCL to a renewed course of MBCT.

Furthermore, it is possible that participants randomized to the control group suffered demoralization, causing their symptoms to worsen (Cunningham, Kypri, & McCambridge, 2013). Letting patients in the control condition start MBCL after the TAU period, alsomeans the current study did not include a follow-up for the TAU condition. We therefore cannot compare the long-term follow-up results between both conditions: consequently, it is unclear how this population fares over time without being offered MBCL. Finally, the single-centre design might have reduced the generalisability of our findings so it will be important to replicate these findings in a multi-centre context.

6.3. Clinical and research implications

With regard to the clinical implications of our study, we must first address the two suicides that occurred in the initial phase of the RCT, even though they did not seem to be related to participation in the study. Based on our experience, even though the prevention of suicide cannot be guaranteed, we conclude that in this population active monitoring of suicidal ideation should take place at each study

assessment. If patients express signs of increased suicide risk, the regular procedures, i.e. direct contact with the psychiatrist on duty or emergency unit, should be put in place.

Based on the current study, MBCL seems useful to implement as an additive approach to improve depression levels and quality of life. From a clinical perspective, however, offering MBCL as an additive treatment to MBCT has the disadvantage that only patients who have already followed MBCT can participate, and MBCT is not yet widely available. An alternative approach to the sequential treatment design would be to investigate whether MBCL might work better as a first step for patients with depression, or perhaps a subsample of them. For example, those with high levels of self-criticism might benefit from a more explicit approach to self-compassion early on. Especially in terms of cost-effectiveness, this approach would be another interesting avenue for future research. Additionally, cost-effectiveness is interesting to investigate further as MBCL participants made less use of health care services during MBCL, apart from general practitioners.

To optimise the (sequential) treatment trajectory, we recommend replicating our study in a prospective sequential trial, comparing MBCT + MBCL to MBCT only, or possibly using MBCT as active control to MBCL to correct for the potential 'double dosage' effect. As an earlier age of onset and younger age seem to be associated with a better outcome, MBCL may be particularly suitable for this subset of patients. So, future trials should include these as moderating variables to test this hypothesis. More generally, it would be interesting to further explore how MBCT and MBCL fit in with current available treatments, and whether and how they could be sequenced with CBT or (m)ADM.

Author Contribution

Ms. Schuling was involved in the design of the trial, the collection, analysis and interpretation of data and in writing and submitting the paper. Dr Huijbers was involved in the design of the trial, the analysis and interpretation of data and in writing the paper. Dr Van Ravesteijn was involved in the design of the trial, the collection and interpretation of data and in writing the paper. Ms. Cillessen was involved in the analysis and interpretation of the follow-up data and in writing the paper. Dr Donders was involved in the analysis of data and in writing the paper. Professor Kuyken was involved in the interpretation of data and in writing the paper. Professor Speckens was involved in the design of the trial, the analysis and interpretation of data and in writing the paper.

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Declaration of Competing Interest

The clinical research team declares it had no part in developing the MBCL programme, though Prof. Speckens and Ms. Schuling made modifications to it in collaboration with the original developers following the pilot study (Schuling et al., 2017). The team does not gain income from the sale of books on MBCL, nor does it gain income from giving lectures or workshops about it. Prof. Speckens is founder and clinical director of the Radboudumc Centre for Mindfulness. Ms. Schuling, Dr Van Ravesteijn, Dr Huijbers and Ms. Cillessen are affiliated with the Radboudumc Centre for Mindfulness. Dr Donders is affiliated with the Radboudumc Biostatistics department. Prof. Kuyken is director of the Oxford Mindfulness Centre and funded by the Wellcome Trust (107496/Z/15/Z).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.03.182.

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