MINDFULNESS-BASED COGNITIVE THERAPY IN COPD: A CLUSTER-RANDOMISED CONTROLLED TRIAL

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"Take home" message: Mindfulness-based cognitive therapy is an efficacious add-on to PR programs to reduce psychological distress in COPD

ABSTRACT

A considerable proportion of patients with chronic obstructive pulmonary disease (COPD) entering pulmonary rehabilitation (PR) report psychological distress, which is often accompanied by poor physical health status. Mindfulness-based cognitive therapy (MBCT) has been shown to improve psychological and physical outcomes in other chronic diseases. We therefore evaluated the efficacy of MBCT as an add-on to a standard pulmonary rehabilitation (PR) program in COPD.

COPD patients eligible for PR were cluster-randomised to receive either an 8-week, group-based MBCT program as an add-on to an 8-week PR program (n=39), or PR alone (n=45). The primary outcomes of psychological distress and physical health status impairment were measured with the Hospital Anxiety and Depression Scale (HADS) and the COPD Assessment Test (CAT) before randomisation (T1), mid- (T2) and post-intervention (T3), and at three (T4) and six months' follow-up (T5).

A statistically significant time×arm effect was found for the HADS (Cohen's *d*=0.62, 95% CIs (*d*)=0.18–1.06, *p*=0.010). The treatment effect on the CAT failed to reach statistical significance (*d*=0.42, 95% CIs (*d*)=-0.06–0.90, *p*=0.061).

MBCT showed a statistically significant and durable effect on psychological distress, indicating that MBCT may be an efficacious add-on to standard PR-programs in COPD.

Keywords: chronic obstructive pulmonary disease, cluster-randomised controlled trial, mindfulness-based cognitive therapy, physical health status impairment, psychological distress, psychosocial intervention.

INTRODUCTION

A considerable proportion of patients with chronic obstructive pulmonary disease (COPD) entering pulmonary rehabilitation (PR) report clinically significant levels of psychological distress in the form of anxiety (32%) and depression (27%) [1]. Psychological distress is often undertreated in COPD, and is associated with poor physical outcomes, including physical health status impairment, low physical activity levels and inflammation [2,3]. The efficacy of psychopharmacological treatment in COPD is limited and patients are often reluctant to take additional medication [4,5]. Psychosocial intervention has been suggested as an alternative or complementary treatment strategy for reducing psychological distress and physical impairment [3,6]. This approach is supported by a recent meta-analysis of controlled trials of psychosocial interventions showing reduced psychological distress in COPD – particularly when interventions included cognitive elements [7]. Additionally, another recent meta-analysis [8] indicates that relaxation and meditative techniques have the potential to improve both physical and psychological outcomes in COPD. Taken together, psychosocial interventions that combine cognitive and meditative elements may be effective in improving both psychological and physical outcomes in COPD.

Mindfulness-based cognitive therapy (MBCT) [9] is a group-based intervention that integrates mindfulness meditation with elements of cognitive behavioural therapy (CBT). MBCT aims to assist the patient in recognising maladaptive cognitions, emotions and bodily sensations, and relating to them in a non-judgmental and compassionate manner. In contrast to another popular mindfulness-based intervention, mindfulness-based stress reduction (MBSR), which primarily consists of meditative elements, the combination of cognitive therapy and meditative training in MBCT may be a helpful approach to reduce the self-blaming, catastrophising cognitions and misinterpretations of bodily sensations (e.g. breathlessness) that have been linked to patterns of anxiety, demobilisation and depression in COPD [10,11]. MBCT has been shown to improve psychological and physical outcomes in other chronic diseases [12], and could be hypothesized to also be effective in COPD. To date, only two studies of relatively limited methodological quality, i.e., a small pilot study [13] and an RCT with a gender-biased sample [14], have explored the efficacy of mindfulness-based intervention in COPD. The effects found for respiratory rate, emotional function [13], dyspnoea and health-related quality of life [14] did not reach statistical significance or were in the opposite of the expected direction. Both studies used MBSR, and no studies so far have explored the efficacy of MBCT in COPD.

The aim of the present study was therefore to test the efficacy of MBCT as an add-on to a standard pulmonary rehabilitation (PR) program in improving the primary outcomes of psychological distress and physical health status impairment in COPD. Our secondary hypotheses were that MBCT would lead to heightened activity levels measured by accelerometers and reduction of the expression of the inflammatory cytokines interleukin 6 (IL-6), IL-8, tumour necrosis factor alpha (TNF-α) and IL-17E. These cytokines have previously been shown to be induced by psychological distress [15], play a role in COPD pathology [16] and reduced with mindfulness-based intervention [17]. Additionally, we explored the possible moderating effects of age, gender, MBCT attendance rate and patients' perception of the therapeutic working alliance, together with the potential mediating effects of mindfulness, self-compassion, breathlessness catastrophising and COPD-specific self-efficacy.

METHODS

The study was a cluster-randomised controlled trial conducted at Aarhus University Hospital, Denmark, with the intervention arm receiving MBCT as an add-on to a standard PR program (MBCT+PR) and the active control arm receiving PR only. PR classes were group-based and served as units of randomisation. The cluster-randomised design was chosen to avoid the risk of contamination bias if individual patients attending the same PR group were randomised to the MBCT+PR and PR-only arms, respectively. As all outcomes were relevant to and reported by individual patients, study objectives pertain to the individual level. Ethical approval was obtained from The Central Denmark Region Committee on Health Research Ethics and the trial was pre-registered at ClinicalTrials.gov (#NCT02042976).

Participants

COPD patients referred to PR at Aarhus University Hospital from February 2014 to January 2016 were invited to take part in the study. At the cluster level, all PR classes held at Aarhus University Hospital after the study initiation date were eligible for inclusion. At the individual patient level, inclusion criteria were: 1) a spirometry-confirmed (FEV1 <50%) COPD diagnosis together with a Medical Research Council (MRC) dyspnoea score of ≥3 and 2) physical capability to attend the exercise component of PR. Exclusion criteria were: 1) a comorbid diagnosis of apoplexia, dementia or unstable coronary heart disease and 2) inability to speak or understand Danish. After receiving written and oral information and providing written consent, patients completed the first

questionnaire package. Patients were then allocated to a PR group (cluster), which was then randomised following the procedure described below.

Randomisation and blinding

PR groups were cluster-randomised to either MBCT-PR or PR-only. A random allocation sequence of 12 units, corresponding to the planned number of PR groups to be enrolled in the study, was generated by an independent researcher prior to data collection using Power and Sample Size Software (PASS), v.12 (NCSS, Kaysville, UT). Researchers and clinicians involved in patient recruitment were blind to the allocation sequence, which was kept under lock. Due to the nature of psychosocial interventions, patient blinding could not be maintained throughout the intervention, and two to seven days before the first session of a new PR class, information about the study arm allocation of that particular PR group was provided to patients, research assistants and clinicians.

Treatment arms

The standardised MBCT program tested in the present study included one 30-60 minute individual telephone-interview followed by eight weekly 105-minute group sessions of meditation and educational cognitive exercises. The program was originally developed to prevent relapse in previously depressed individuals [9]. An adapted treatment manual was developed and piloted with a group of four COPD-patients prior to initiation of the present trial (see Table 1 for an overview, and see the supplementary material for the complete manual). This resulted in four COPD-specific modifications: 1) focus on the heartbeat, the blood-flow and the feet's contact with the ground as means of meditational stabilisation instead of the breath, 2) reduced length and intensity of meditation exercises and home practice, 3) reduced complexity of cognitive exercises and 4) exclusion of the whole-day retreat. The intervention was conducted by a clinical psychologist (IF-V). Group-sizes varied from three to thirteen depending on the number of consenting patients assigned to the respective PR group. Weekly handouts and an audio compact disc with meditation exercises were provided to each patient for between-session practice.

[Insert Table 1 near here]

The PR program consisted of two weekly sessions over an eight-week period. One weekly session lasted 90 minutes, with physical exercise only. The other weekly session lasted 150 minutes and included physical exercise and disease- and lifestyle-oriented education. The program followed the guidelines of the American Thoracic Society and the European Respiratory Society [18].

In the MBCT+PR arm, MBCT was added to the PR program after each of the eight weekly 90-minute sessions.

Measures

Primary outcome measures

Psychological distress was assessed using the Hospital Anxiety and Depression Scale (HADS) [19]. Total scores range from 0-42 with higher scores representing higher levels of psychological distress. Internal consistency (Cronbach's α) was 0.82 in the present sample [20]. The COPD Assessment Test (CAT) [21] was used to assess physical health status impairment. Total scores range from 0-40 with higher scores representing higher levels of physical health status impairment. The measure has shown satisfactory psychometric properties (α=0.92) [22]. Data were collected pre- (T1), mid- (4 weeks after first session) (T2) and post-intervention (8 weeks after first session) (T3) as well as at three (T4) and six months (T5) after the final session.

Secondary outcome measures

Daily physical activity was measured with triaxial accelerometers (ActiGraph Monitor wGT3X-BT) carried around the waist for two periods of seven days (T1 and T3). The accelerometers stored data at 80Hz with 10s epochs (ActiLife Analysis Software, Maribo Medico). Data were considered valid if the wear time was ≥10 hours per day for ≥4 days [23]. The average mid-day (10AM to 4PM) activity level was calculated for each patient at T1 and T3 and expressed as vector magnitude counts per minute (VMcpm, the vectorial sum of activity in the three orthogonal directions measured over a one-minute period) [24]. For analyses of inflammatory cytokines, whole blood samples were collected into 6 ml tubes (PAXgene) at T1 and T3. RT-PCR was carried out as previously described [25], using the following primers: TNF-α (Hs01113624_g1), IL-6 (Hs01075666_m1), IL-8 (Hs00174103-m1), IL-17E (Hs03044841_m1) and 18s (Hs03003631_g1).

Moderators

Age and gender were registered at T1. Number of MBCT sessions attended was registered for each patient in the MBCT+PR arm at T3. Patients' individual perceptions of the therapeutic working alliance was assessed with the Working Alliance Inventory (WAI) [26] at T2, and patients were asked to keep a diary of frequency and duration of meditation practice between sessions.

Mediators

Mindfulness (Five-Facet Mindfulness Questionnaire (FFMQ) [27]), self-compassion (Self-

Compassion Scale (SCS) [28]), breathlessness catastrophising (Breathlessness Catastrophizing Scale (BCS) [29]) and COPD-specific self-efficacy (COPD Self-Efficacy Scale (CSES) [30]) were measured at all time points. FFMQ total scores consisted of four out of five facets [31].

Statistical analysis

A priori sample-size calculations indicated that 2×56 patients would be sufficient to detect an average 3-point reduction in CAT scores after PR with 80% statistical power (two-sided alpha: 5%) [32]. In addition, the chosen sample size would also allow for detection of a between-group minimal clinically important difference (MCID) in HADS scores over time of 20% [20] with a statistical power of 78%. Missing items were substituted with the patient's average response on the remaining scale items, if the patient had completed ≥50% of the items [33].

Mixed linear models (MLMs) were chosen to compare MBCT+PR and PR-only over time on the primary outcome variables and the secondary outcome variable of activity level, based on the intent-to-treat sample. We specified both two- (time nested within individuals) and three-level models (time nested within individuals nested within clusters). Due to non-convergence of models, final models were specified with only two levels. However, there was no time×cluster differences over time on primary outcomes (HADS: p=0.799; CAT: p=0.209). Time was entered as a log-transformation of the time points (i.e., 1 through 5 [34]). An intervention effect was indicated by a statistically significant two-way interaction between arm and time. Treatment moderators were explored as either two-way interaction terms (time×moderator) in the MBCT+PR arm only – when measures were only available in the MBCT+PR arm (i.e., attendance rate and working alliance) – or three-way interaction terms (time×arm×moderator) when measures were available in both arms (i.e., gender and age). Effect sizes were expressed as Cohen's d derived from the F-test calculated as $d=2*\sqrt{(F/df)}$ [35]. All MLMs were estimated with the maximum likelihood method.

In case of a detected effect of MBCT+PR, the FFMQ, the SCS, the BCS and the CSES were explored as mediators in time-lagged analyses [36] where the mediator at $time_x$ predicted the outcome at time $_{x+1}$, controlling for the outcome variable at $time_x$ and the mediator at $time_{x-1}$. In case of a significant result, the reverse pattern was also explored in order to test for reciprocal relations. These analyses were conducted on the MBCT+PR group only, where five observation points were available.

Statistical analyses of the fold change in cytokine mRNA expression levels were carried out using Graph Pad software version 6. Two-way ANOVAs were used to compare cytokine mRNA fold change values in the MBCT+PR and PR-only arms from T1 to T3. We also examined correlations between the change in mRNA cytokine expression levels and the change in HADS scores from T1 to T3.

The statistical analyses were conducted with IBM SPSS statistics version 24 and Stata version 14.

RESULTS

Participant characteristics

From February 20, 2014, to January 15, 2016, 84 out of 161 patients assessed for eligibility (52%) in 12 clusters consented to participate in the trial (Figure 1). Sixty patients declined participation (37%) and 17 were ineligible (11%). Fourteen patients from the intent-to-treat exposed population withdrew from the study, and 12 patients failed to return questionnaires after two unanswered telephone reminders. Eligible patients who declined participation in the study (n=60) did not differ statistically significantly from participants in terms of gender, but were statistically significantly older (mean age: 71.9 yrs vs. 67.2 yrs, p=0.002). Average PR-attendance did not differ significantly between the MBCT+PR (Mean=10.7 sessions) and PR-only (Mean=10.0 sessions) arms (p=0.434), and was generally comparable to the attendance rate reported in an evaluation of the PR-service at Aarhus University Hospital, with 55 patients out of 120 completing the program (unpublished data).

[Insert Figure 1 near here]

Baseline characteristics are shown in Table 2. The treatment arms were well-balanced with regard to demographics, clinical characteristics, outcome variables and cluster characteristics, the only exception being use of complementary and alternative medicine over the last year. At baseline, 27.4% of the total sample had clinically significant anxiety levels (≥10 points on the HADS Anxiety subscale) and 19% had clinically significant depressive symptoms (≥10 points on the HADS Depression subscale).

[Insert Table 2 near here]

Primary outcomes

Means and SDs for the primary outcomes across all time points are shown in Table 3 together with the effects. No main effect of time was found for the HADS (Cohen's d=0.13, p=0.616) or the CAT (d=0.16, p=0.293). In contrast, a statistically significant time×arm effect was found for the HADS, corresponding to a medium effect size. The effect for the CAT was smaller and did not reach statistical significance. When adjusting the results for multiple comparison with the Benjamini-Hochberg correction, the effect on the HADS remained statistically significant. Two types of sensitivity analyses were then performed for this significant result. First, when analysing the possible association of HADS scores at baseline with subsequent study dropout with logistic regression, no effect was found (p=0.932). In addition, when testing the robustness of the observed effect on the HADS with an MLM with the last observation carried forward (LOCF) for study dropouts, the effect remained significant (d=0.53, p=0.021).

Intra-cluster correlation coefficients (ICCs) were 0.02 and 0.21 for the HADS and the CAT, respectively. Supplementary analyses of the HADS Depression and Anxiety subscales showed a statistically significant time×arm effect on depression, but not anxiety (Table 3).

[Insert Table 3 near here]

Secondary outcomes

A statistically significant increase in TNF-α mRNA from T1 to T3 was found in the PR-only arm, while TNF-α remained unchanged in the MBCT+PR arm (Figure 2). The between-arm differences did not reach statistical significance. No statistically significant changes were found in IL-6 and IL-8 mRNA from T1 to T3. IL-17E mRNA was not detectable in the peripheral blood of any patients at any time point analysed and was therefore not subjected to statistical analysis. Correlations between changes in TNF-α, IL-6 and IL-8 mRNA and change in HADS scores were 0.03, 0.05 and 0.008 for MBCT+PR (n=19) and 0.0053, 0.08 and 0.08 for PR-only (n=19). Supplementary analyses of frequency of hospitalizations (p=0.213) and exacerbations (p=0.904) indicated no statistically significant time×arm effects at T5. The effect on activity level did not reach statistical significance.

[Insert Figure 2 near here]

Moderators

A moderating effect of age was found for the effect on the HADS (F=4.3, p=0.040; d=0.38), indicating a better outcome for younger patients. The moderating effects of gender (d=0.31, p=0.096), the WAI (d=0.83, p=0.072) and attendance rate (d=0.19, p=0.579) did not reach statistical significance. Only three patients in the MBCT+PR arm completed meditation practice diaries, and the data was therefore not subjected to statistical analysis.

Mediators

Changes in self-compassion (SCS) significantly preceded changes in HADS scores (Table 4). The reverse pattern was not significant, (B=0.20, p=0.227). Changes in the FFMQ, the BCS and the CSES were not significant predictors of subsequent change in the HADS.

[Insert Table 4 near here]

DISCUSSION

Our main findings indicated that MBCT as an add-on to PR led to a clinically relevant reduction (1.5 points [20]) in psychological distress in COPD (d=0.62). The effect size was larger than the previously found pooled effect size for psychosocial intervention in COPD (Hedges' g=0.38) [7], and was maintained six months after termination of the 8-week intervention period. Our results are in disagreement with the earlier studies of mindfulness-based interventions, which found no statistically significant effects on the psychological outcomes of anxiety and perceived stress in COPD [13,14]. Additional analyses suggested that MBCT relieved psychological distress primarily by reducing symptoms of depression, rather than anxiety, which may explain the null-findings in earlier studies. Furthermore, the interventions evaluated in earlier studies did not include cognitive elements, and combining elements from mind-body interventions and CBT in the MBCT program for COPD may therefore be more effective than mindfulness-meditation only [7]. Our results should be interpreted with caution, as a psychological control component was not added to the PR program in the control arm (PR-only). A statistical trend-wise effect was observed for physical health status impairment (d=0.42, p=0.061). This effect did not reach a clinically relevant level (a 2.0 point reduction [22]), but was, however, comparable to the pooled effect size previously found for effects of mind-body interventions on physical outcomes in COPD (g=0.40) [7]. The statistically near-significant effect for this outcome could therefore possibly be explained by the smaller than planned sample-size obtained within the time-frame of the present study. There was no effect of time across

treatment arms, which was unexpected, as both arms received a standard PR program previously shown to reduce psychological distress and physical health status impairment [18]. A possible explanation could be that PR prevented a worsening of outcomes, which could otherwise have been the result of the progressive disease of COPD. As PR is part of standard COPD care, it would have been unethical to include a study arm that did not receive PR.

A statistically significant increase in TNF-α from before to after treatment was found in the PR-only control arm, while no changes were observed in MBCT+PR participants. This could indicate that MBCT prevented the exacerbation of TNF-α mediated inflammation over time. In correspondence with our findings, mindfulness practice has previously been shown associated with larger reductions in TNF- α after stress-induction in healthy individuals [17]. This specific cytokine is believed to play a role in lung diseases, and inhibiting TNF-α has been proposed as a relevant therapeutic target in inflammatory diseases [37]. Adverse side effects of pharmacological TNF-α inhibitors such as pain and diarrhea are common in COPD, suggesting the potential relevance of MBCT as an alternative in inflammation control [37]. No effects were found for the remaining inflammatory markers of IL-6, IL-8 and IL-17E. Our use of peripheral blood cells as a biological source of pro-inflammatory cytokine, as opposed to cells from the lung microenvironment, might explain the lack of mRNA expression of these specific cytokines. Examination of tissue resections or broncoalveolar lavage fluid could perhaps have yielded different results. Our results should therefore be considered preliminary and require further examination in future studies.

No statistically significant effect of the intervention was found for patients' activity levels as measured with accelerometers. In addition to the possibility of insufficient statistical power for this secondary variable, another explanation could be that it takes more than eight weeks of training for patients to implement the complex behaviour changes needed to observe changes in their average physical activity level [18]. Longer follow-up periods could thus be relevant for activity monitoring in future studies.

Our additional results suggest that age moderates the effect of MBCT on psychological distress, with MBCT appearing to be more effective for younger COPD patients. This is in line with a review stating that younger COPD-patients may be more adept at learning the skills and tools taught in psychosocial intervention [38]. This finding may guide clinicians when referring patients to MBCT. The moderating effects of gender, MBCT attendance rate and therapeutic working alliance did not reach statistical significance. The non-significant effect of gender differs from the results

reported in the COPD literature of gender differences in medical and behavioural treatment adherence and outcomes [39]. Concerning MBCT attendance, the reasons for non-attendance may vary, including perception of sufficient treatment gain or perceived difficulties in relation to the intervention, which could explain the lack of a moderating effect. We attempted to assess the frequency of home practice, but the number of completed home practice diaries in the present sample was insufficient. Taking the large effect size of therapeutic working alliance into account (d=0.83), the non-significant result for this moderator could be due to the relatively limited number of patients in the MBCT+PR arm (n=39).

The results of our exploratory mediational analyses suggest that the effect of MBCT on psychological distress may be facilitated through increased levels of self-compassion. Our finding suggests that stimulating a non-judgmental attitude through mindfulness meditation and cognitive exercises may be efficacious in relieving psychological distress in COPD, a disease where feelings of smoking-related self-blame and stigma are highly prevalent and associated with depression [40]. However, other potential mechanisms driving the effect of MBCT in COPD cannot be excluded, and future research should implement more assessment points, e.g., at every session, in order to capture more fine-grained dynamics of change.

The present study has several strengths, including a randomised design and a long-term (six month) follow-up. However, a number of limitations should also be noted. First, as an attention control condition was not added to the PR program in the PR-only arm, we cannot rule out that additional attention from health care professionals may have boosted the effect in the MBCT+PR arm. On the other hand, the validity of our findings are supported by controls receiving an active intervention previously shown to be effective [18]. Second, due to a lower inclusion rate than expected, the final sample-size was smaller than projected, which could explain the statistically non-significant effect (p=0.061) found for physical health status impairment. The limited enrolment rate could perhaps be due to that not all patients eligible for PR reported clinically significant levels of psychological distress. Third, patients who declined participation in the study were older than participating patients, which could limit the external validity of our results. Fourth, attrition rates were high in both the intervention and the control arm. This is a general issue in COPD research and practice where compliance rates generally are poor [41]. Dropout, however, was balanced across treatment arms and did not appear, as supported by our sensitivity analyses, to compromise the robustness of the results. Finally, the single-site design with only one MBCT-instructor and one team of PR

providers may limit the generalisability of the results. Taken together, to increase validity of the results, future multi-site trials including larger samples and attention control arms are recommended.

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Table 1: **Overview of the COPD-specific MBCT-program**

Session	Theme	Mindfulness exercises	Cognitive exercises	Home work
1	”Awareness and automatic pilot”	”The raisin exercise”; ”The body scan”	-	“The body scan” every day; mindfulness of a routine activity
2	”Living in our heads”	”Awareness of the heartbeat and the blood flow”	“Thoughts and feelings exercise” (noticing connection between thoughts and emotional states); introduction of “the pleasant experiences calendar” (monitoring daily activities and their effects on thoughts, emotions and bodily sensations)	”Awareness of the heartbeat and the blood flow” every day; mindfulness of a routine activity; complete “the pleasant experiences calendar”
3	”Gathering the scattered mind”	”Awareness of the heartbeat, blood flow and body”; “The 3-min breathing space”; “Mindful stretching”	Review of “the pleasant experiences calendar”; introduction of “the unpleasant experiences calendar” (monitoring daily activities and their effects on thoughts, emotions and bodily sensations)	“Mindful stretching” every day; “the 3-min breathing space” 3 pre-scheduled times per day; complete “the unpleasant experiences calendar
4	”Recognising aversion”	”Awareness of the heartbeat, blood flow, body, sounds and thoughts”; “the 3-min breathing space”	Review of “the unpleasant experiences calendar”; “automatic thoughts exercise” (noticing negative automatic thoughts and their effects on emotions and bodily sensations, and knowing when to do a 3-min breathing space)	“Awareness of the heartbeat, blood flow, body, sounds and thoughts” every day; “the 3-min breathing space” every time something uncomfortable happens”
5	”Allowing/letting be”	”Being with the difficult”; ”Walking meditation”; “the 3-min breathing space”	-	“Being with the difficult” every day; “the 3-min breathing space” every time something uncomfortable happens”
6	”Thoughts are not facts”	”Awareness of thought and the emotional reaction”; “the 3-min breathing space”	“Mood, thoughts and alternative viewpoints exercise” (our mood can influence how we think about/interpret a situation); “My personal warning system” (noticing personal signals of bad mood and anxiety)	Mindfulness exercise of own choice every day; “the 3-min breathing space” every time something uncomfortable happens”; complete “my personal warning system”
7	”How can I best take care of myself?”	“Awareness of spontaneous reactions of body, emotions, thoughts”; “the 3-min breathing space”	Review of “the personal warning system”; “Activities and mood exercise” (noticing connections between daily activities and mood); introduction of “the action plan” (a personal plan how to best schedule activities when emotions threaten to overwhelm”	Use the mindfulness exercises that you are planning to use after the program has ended; complete the personal “action plan”
8	”Maintaining and extending new learning”	“The body scan”	Review of “the action plan”	-

See supplementary material for the complete manual. COPD=Chronic obstructive pulmonary disease. MBCT=Mindfulness-based cognitive therapy.

***Table 2*: Baseline characteristics of the intention-to-treat population**

	Total (n=84)	**Intervention (n=39)**	**Control (n=45)**	***p****
Age (yrs)	67.2 (7.74)	66.67 (8.03)	67.67 (7.54)	0.558
Gender				0.449
Women	48 (57.1%)	24 (61.5%)	24 (53.3%)	
Men	36 (42.9%)	15 (38.5%)	21 (46.7%)	
Marital status (n=82)				0.673
Married/cohabiting	40 (48.8%)	19 (51.4%)	21 (46.7%)	
Single/widow(er)	42 (51.2%)	18 (48.6%)	24 (53.3%)	
Educational level (n=81)				0.986
Lower (<2 yrs of further educ.)	61 (75.3%)	28 (75.7%)	33 (75.0%)	
Medium (2-4 yrs of further educ.)	18 (22.2%)	8 (21.6%)	10 (22.7%)	
Long (≥5 yrs of further educ.)	2 (2.5%)	1 (2.7%)	1 (2.3%)	
Occupational status (n=80)				0.928
Full- or part-time work	4 (5.0%)	2 (5.6%)	2 (4.5%)	
Unemployed	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Retired	72 (90.0%)	32 (88.9%)	40 (90.9%)	
Sick leave	4 (5.0%)	2 (5.6%)	2 (4.5%)	
Attitude towards psychotherapy	3.58 (1.07)	3.55 (1.26)	3.61 (0.92)	0.824
Use of psychological support during the last year (n=82)	13 (15.9%)	5 (13.5%)	8 (17.8%)	0.559
Yes	69 (84.1%)	32 (86.5%)	37 (82.2%)	
No				
Use of CAM treatment during the last year (n=79)				0.042
Yes	18 (22.8%)	4 (11.8%)	14 (31.1%)	
No	61 (77.2%)	30 (88.2%)	31 (68.9%)	
Knowledge about mindfulness (n=79)				0.527
Yes	22 (27.8%)	11 (31.4%)	11 (25.0%)	
No	57 (72.2%)	24 (68.6%)	33 (75.0%)	
FEV_1 (% predicted)	37.74 (11.76)	37.50 (12.09)	37.94 (11.62)	0.872
MRC	3.59 (0.86)	3.56 (0.89)	3.63 (0.84)	0.744
BMI	25.75 (6.70)	25.88 (7.25)	25.63 (6.29)	0.893
Comorbidity				
Cancer (n=83)	10 (12.0%)	6 (15.8%)	4 (8.9%)	0.336
Heart condition (n=83)	38 (45.8%)	18 (47.4%)	20 (44.4%)	0.790
Osteoporosis (n=83)	37 (44.6%)	15 (39.5%)	22 (48.9%)	0.390
Smoking (n=81)				0.807
Yes	23 (28.4%)	11 (29.7%)	12 (27.7%)	
No	58 (71.6%)	26 (70.3%)	32 (72.3%)	
Type of treatment				
ICS (n=82)	70 (85.4%)	31 (83.8%)	39 (86.7%)	0.713
LABA (n=82)	77 (93.9%)	35 (94.6%)	42 (93.3%)	0.812
LAMA (n=82)	80 (97.6%)	35 (94.6%)	45 (100.0%)	0.114
PDE4 inhibitors (n=82)	10 (12.2%)	4 (10.8%)	6 (13.3%)	0.728
Home oxygen use (n=81)	4 (4.9%)	2 (5.6%)	2 (4.4%)	0.819
Antidepressant and/or anxiolytic drug treatment during the last year (n=X)	19 (22.6%)	10 (25.6%)	9 (20.0%)	0.538
CAT total (n=71)	19.06 (7.08)	19.40 (7.21)	18.80 (7.07)	0.729
HADS total (n=82)	13.72 (7.67)	14.04 (7.65)	13.46 (7.77)	0.737
Activity level (VMcpm) (n=62)	389.70 (166.82)	397.11 (144.68)	382.75 (187.29)	0.738
IL-6 (n=38)	1.59 (1.57)	1.54 (1.67)	1.84 (1.53)	0.840
IL-8 (n=38)	1.48 (1.90)	1.10 (2.28)	1.40 (1.48)	0.660
TNF-α (n=38)	0.96 (0.50)	0.84 (0.35)	1.08 (0.60)	0.210
Number of PR group (clusters)	12	6	6	-
PR group (cluster) size	7.00 (2.73)	6.50 (1.87)	7.5 (3.51)	0.552

Continuous data are mean (SD) and categorical data is number (%). BMI=body-mass index. CAT=COPD Assessment Test. CAM=complementary and alternative medicine. FEV_1=forced expiratory volume in 1 second. HADS=Hospital Anxiety and Depression Scale. ICS=inhaled corticosteroids. LABA=long-acting β2-agonists. LAMA=long-acting muscarinic antagonists. MRC=Medical Research Council dyspnoea score. PDE4=phosphodiesterase 4. VMcpm=vector magnitude counts per minute. *) Independent samples t-tests for continuous variables, chi^2-tests for categorical variables.

***Table 3*: Primary outcomes and effect**

	Baseline		Mid-intervention		Post-intervention		3 mo. FU		6 mo. FU	
	MBCT+PR	PR	MBCT+PR	PR	MBCT+PR	PR	MBCT+PR	PR	MBCT+PR	PR
HADS										
Mean (SD)	14.04 (7.65)	13.46 (7.77)	13.18 (7.20)	13.71 (6.66)	12.13 (7.08)	14.18 (8.24)	12.08 (6.21)	15.34 (6.95)	12.46 (5.72)	14.74 (8.26)
N	37	45	30	36	30	37	24	33	25	33
	Time x arm interaction: F=6.9, *p*=0.010; Cohen's *d*=0.62; 95%CI (*d*): 0.18–1.06									
CAT										
Mean (SD)	19.40 (7.21)	18.80 (7.07)	21.38 (5.77)	21.09 (6.15)	18.55 (7.19)	17.39 (4.95)	19.25 (5.94)	21.47 (6.21)	19.30 (6.17)	20.55 (7.18)
N	30	41	31	35	20	18	25	34	25	33
	Time x arm interaction: F=3.6; *p*=0.061; Cohen's *d*=0.42; 95%CI (*d*): -0.06–0.90									
Supplementary analyses										
HADS-D										
Mean (SD)	6.32 (3.67)	5.90 (4.10)	5.78 (3.57)	5.91 (3.47)	5.33 (3.77)	6.26 (4.60)	5.42 (3.98)	7.17 (3.93)	5.45 (3.03)	6.76 (4.82)
N	37	45	30	36	30	37	24	33	25	33
	Time x arm interaction: F=2.3; *p*=0.136; Cohen's *d*=0.51; 95% CI (*d*): 0.07-0.95									
HADS-A										
Mean (SD)	7.72 (4.72)	7.57 (4.12)	7.40 (4.22)	8.09 (4.17)	6.80 (3.86)	7.92 (4.16)	6.67 (2.81)	8.17 (3.60)	7.01 (3.44)	7.99 (4.21)
N	37	45	30	37	30	37	24	33	25	33
	Time x arm interaction: F=7.1; *p*=0.009; Cohen's *d*=0.26; 95% CI (*d*): -0.18-0.70									

CAT=COPD Assessment Test. FU=follow-up. HADS=Hospital Anxiety and Depression Scale-Total score. HADS-A=Hospital Anxiety and Depression Scale-Anxiety subscore. HADS-D=Hospital Anxiety and Depression Scale-Depression subscore. MBCT=mindfulness-based cognitive therapy. PR=pulmonary rehabilitation.

***Table 4*: Mediators of the effect on HADS**

	Baseline		Mid-intervention		Post-intervention		3 mo. FU		6 mo. FU	
	MBCT+PR	PR	MBCT+PR	PR	MBCT+PR	PR	MBCT+PR	PR	MBCT+PR	PR
FFMQ										
Mean (SD)	102.51 (11.64)	104.49 (14.68)	101.40 (14.29)	103.52 (13.71)	107.31 (12.84)	103.53 (12.43)	106.77 (12.47)	102.57 (13.46)	107.43 (14.11)	104.65 (14.03)
N	33	41	30	32	29	35	25	32	24	31
	Time-lagged analysis: B=0.05, *p*=0.424, 95% CIs (B)=-0.07–0.17									
SCS										
Mean (SD)	39.53 (5.46)	40.22 (6.09)	39.00 (7.26)	38.58 (5.15)	40.36 (5.87)	39.13 (5.15)	41.13 (6.16)	39.00 (6.42)	39.78 (5.92)	38.16 (5.94)
N	34	37	25	33	25	32	24	29	23	31
	Time-lagged analysis: B=0.24, *p*=0.035, 95% CIs (B)=0.02–0.46									
BCS										
Mean (SD)	26.35 (13.39)	22.04 (11.63)	22.93 (12.36)	22.24 (10.24)	19.34 (11.96)	21.64 (10.25)	17.77 (10.23)	22.91 (12.19)	18.52 (10.69)	22.66 (13.22)
N	37	42	30	34	30	36	25	32	24	32
	Time-lagged analysis: B=0.01, *p*=0.878), 95% CIs (B)=-0.12–0.14									
CSES										
Mean (SD)	90.72 (23.94)	92.05 (22.57)	91.10 (23.16)	93.97 (23.30)	95.52 (27.03)	94.53 (22.53)	95.04 (28.16)	90.44 (22.84)	91.32 (27.46)	91.86 (23.24)
N	32	41	25	33	27	33	24	32	24	32
	Time-lagged analysis: B=0.03, *p*=0.337, 95% CIs (B)=-0.03–0.08									

BCS=Breathlessness Catastrophizing Scale, range: 0 (low catastrophising) to 52 (high). CSES=COPD Self Efficacy Scale, range: 34 (low self-efficacy) to 170 (high). FFMQ=Five-Facet Mindfulness Questionnaire, range: 31 (low mindfulness) to 155 (high). FU=follow-up. MBCT=mindfulness-based cognitive therapy. PR=pulmonary rehabilitation. SCS=Self Compassion Scale, range: 12 (low self compassion) to 60 (high).