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Effectiveness of mindfulness-based cognitive therapy in patients with anxiety disorders in secondary-care settings: A randomized controlled trial

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Abstract

Aim: The purpose of this study was to evaluate the efficacy of mindfulness-based cognitive therapy (MBCT) in a secondary-care setting in which the large majority of patients had already undergone pharmacotherapy but have not remitted. Methods: Subjects aged 20 to 75 years who met the DSM-IV-TR diagnosis of panic disorder, agoraphobia, or social anxiety disorder were randomly assigned to the MBCT group (n = 20) or control group (n = 20). The primary outcome was the difference between the two groups in the mean change before and after the intervention on the State-Trait Anxiety Inventory (STAI). Results were analyzed on the basis of intent-to-treat (ITT), using a mixed-effects model repeated measures. Results: Significant differences were found between the MBCT and control groups in mean change on the STAI state subscale (-10.1 difference, 95% confidence interval -16.9 to -3.2, P<0.005) and STAI Trait Anxiety subscale (difference, −11.7; 95% confidence interval, −17.0 to −6.4; P < 0.001). Conclusion: MBCT was shown to be effective in the secondary-care setting in which the vast majority of patients with anxiety disorders are treatment-resistant to pharmacotherapy.

Keywords: mindfulness-based cognitive therapy, anxiety disorders

Introduction

Kabat-Zinn, J., of the University of Massachusetts, was the first to introduce mindfulness techniques into the medical field. Kabat-Zinn developed an eight-week program called Mindfulness Based Stress Reduction (MBSR) in the 1970s. Influenced by Zen, Kabat-Zinn saw Buddhism not as a religion but as a psychotherapy for solving human problems, and he developed MBSR inspired by his own approach to meditation. When MBSR was first developed, it was mainly targeted at patients with chronic pain, for which no effective treatment had been found in modern medicine, and there were very limited reports on depression and anxiety disorders. For this reason, mindfulness did not receive much attention in the medical field, and even in the 1990s, only a few papers were published each year. This situation changed significantly after Teasdale, J., Williams, M., and Segal, Z. developed mindfulness-based cognitive therapy (MBCT), which integrates cognitive behavioral therapy and MBSR. In 2000, a randomized control trial (RCT) demonstrated the efficacy of mindfulness in preventing the recurrence of depression with three or more episodes 22), bringing mindfulness to the attention of the medical community. Based on these results, clinical guidelines issued by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom recommend MBCT as an effective treatment to prevent the recurrence of depression 15).

MBCT was first shown to be effective in preventing the recurrence of depression, and since then evidence has accumulated for its effectiveness in treating a variety of disorders, including other psychiatric illnesses.

Although research reports on anxiety disorders have been accumulated, they have lagged behind those on depression. In a report published in the 2000s, Lee, S. H. et al. 14) conducted an RCT in 2007 in which 46 subjects meeting diagnostic criteria for generalized anxiety disorder or panic disorder (with or without agoraphobia) were divided into two groups: those undergoing a meditation-based stress management program (intervention group) and a psychoeducational program (control group). The intervention group showed significant improvement in anxiety symptoms.

In 2009, Kim, Y. W. et al.11) conducted

an RCT in which a total of 46 patients with panic disorder or generalized anxiety disorder were randomly assigned to two groups: an MBCT group and a psychoeducation group, and reported that anxiety and depression symptoms were significantly improved in the MBCT group.

Subsequently, in the 2010s, RCTs were reported one after another, showing that MBCT has a significantly favorable effect on anxiety disorders 6)8)12)13)21)24). On the other hand, since most of these studies were conducted in a primary care setting, the implementation rate of pharmacotherapy was low (0-39%). In other words, no study had yet demonstrated the efficacy of MBCT in a secondary-care setting where the vast majority of patients were already on pharmacologic therapy but were not in remission. Therefore, we decided to conduct this study to determine whether MBCT is effective for improving anxiety disorders in a secondary-care setting where many patients are already receiving pharmacotherapy.

I. Aim

The purpose of this study was to evaluate the efficacy of MBCT in a secondary-care setting where the majority of patients were already receiving pharmacotherapy but not in remission.

II. Methods

The study was conducted from October 2014 to July 2015. Forty adult patients (aged 20 to 75 years) attending Keio University Hospital who completed the Structured Clinical Interview for DSM-IV-TR and met the clinical diagnosis of either panic disorder, agoraphobia, or social anxiety disorder were included. Subjects were stratified by STAI-state score, the primary outcome measure, and type of anxiety disorder, and randomly assigned in a 1:1 ratio to the intervention group (MBCT group) or control group (waiting-list group). Allocation was performed at the Clinical Research Center of Keio University School of Medicine, which was not directly involved in the conducting of the study. The study was approved by the Ethics Committee of Keio University School of Medicine.

1. Intervention

The intervention group (20 patients) received standard treatment plus a mindfulness class (an attention training program applying meditation and yoga) for 2 hours every week for a total of 8 sessions. The content was a modified version of the MBCT program conducted at Oxford University and other universities. In addition, home work (mainly meditation and yoga practiced in the classroom) was

conducted for 30-60 minutes every day. The control group (20 patients) received only standard treatment.

2.Outcomes

1) Primary outcome

Changes in mean scores of the State-Trait Anxiety Inventory STAI-state, trait 20) were compared between the two groups at pre- and post-intervention assessments.

2) Secondary outcomes

Kessler 6 (K6) 10), Center for Epidemiologic Studies Depression Scale (CES-D) 17), EuroQol 5 Dimension (EQ-5D) 2), Five Facet Mindfulness Questionnaire (FFMQ) 1), 12-Item Short Form Health Survey (SF-12) 23), Liebowitz Social Anxiety Scale (LSAS) 19), and Mobility Inventory for Agoraphobia (MIA) 3) before and after the intervention were compared between the two groups. LSAS and MIA were administered only to subjects with the target disorders: social anxiety disorder, panic disorder, and agoraphobia, respectively.

3. Sample size

The sample size was calculated based on the results of a previous study 4) that investigated the efficacy of MBCT for anxiety disorders. In this study, the end-point average Beck Anxiety Inventory score was 5.2 (SD = 5.4) in the intervention group and 10.3 (standard deviation = 5.7) in the control group. Therefore, the study required 16 patients in each group to have a power of at least 80% at the 5% significance level (one-sided). In addition, we determined that 20 samples (40 in total) were needed to compensate for patient dropout.

Statistical analysis

We used t-tests and $\chi 2$ tests to compare baseline demographic and clinical characteristics between the two groups. Primary and secondary outcomes were analyzed on the basis of intent-to-treat (ITT), using a mixed-effects model repeated-measures approach. The model included intervention group, week, group-by-week interaction, age, and sex as fixed effects.

Stata Version 14 software (StataCorp LLC, College Station, TX, USA) was used for the statistical analysis.

5. Results

Of the 57 screened participants, 40 who met the inclusion criteria, provided consent, and completed baseline assessments were included in the study. Twenty were randomly assigned to the MBCT group and 20 to the control group. One participant in the MBCT group dropped out during the intervention, and one participant in the control group dropped out after baseline assessment. The two groups had equal dropout rates.

Table 1 shows baseline demographic and clinical characteristics.

The mean duration of treatment from the onset of anxiety disorder was 151.2

± 123.3 months, and the mean duration of treatment was 110.7 ± 118.7 months. Thirty-eight (95%) participants were prescribed a mean of 2.9 psychotropic medications, and 27 (67.5%) participants were prescribed at least one antidepressant medication at the baseline.

There were no significant differences between the two groups in any of the variables, including: age, sex, diagnosis, clinical measures, and mean time from the onset of anxiety disorder to treatment.

1) Primary outcome

Differences in mean changes of scores for the STAI State Anxiety subscale (difference, −10.1; 95% confidence interval, −16.9 to −3.2; P = 0.004) and STAI Trait Anxiety subscale (difference, −11.7; 95% confidence interval, −17.0 to −6.4; P < 0.001) between the MBCT and control groups were significant (Table 2).

(2) Secondary outcomes

There were significant improvements in total scores of FFMQ and K6, and significant differences in the FFMQ subclassification of observing and non-reactivity, but not in non-judging, describing, or acting with awareness. No significant differences were found in CES-D or EQ-5D. In SF-12, there were significant differences in the physical component summary (MCS), but not in the mental component summary (PCS) (Table 2). In the disease-specific measurements, significant improvement was noted in LSAS, while no significant difference was found in MIA.

3) Adverse events

No serious adverse events were observed in either group of participants during the study period.

III. Discussion - including the significance of this paper, difficulties encountered and developments

The results obtained in this study are consistent with the findings of previous studies showing that MBCT reduces anxiety symptoms in patients with anxiety disorders. However, the study is significant in that it demonstrates the effectiveness of MBCT in patients with anxiety disorders in secondary-care settings where the majority of patients have not achieved remission despite many years of pharmacotherapy. For the primary outcomes, there were significant differences not only in STAI-state but also in STAI-trait. This suggests that the effectiveness of MBCT may persist long after the end of the intervention.

On the other hand, there was a significant difference between the two groups in LSAS, but not in MIA. There are two possible reasons why no significant difference was detected in MIA. The first is related to the sample

size. In this study, there were only 15 participants with panic disorder. This may have been a barrier to detecting the effect. The second is the floor effect. The mean baseline score for the MIA's Avoidance Alone subscale in the MBCT group was 1.89±0.52, which was close to the cutoff score (1.61) for a diagnosis of agoraphobia 4). Therefore, we cannot rule out the possibility that the floor effect masked the effectiveness of this intervention.

With regard to the health-related quality of life, no significant improvement was observed in EQ-5D-3L (three levels of severity for each dimension). As Herdman, M. et al. 9) showed, EQ-5D-5L can significantly improve reliability and sensitivity (discriminative power) while maintaining feasibility compared with EQ-5D-3L. EQ-5D-5L was able to significantly improve reliability and sensitivity (discriminatory power) and potentially reduce the ceiling effect, while maintaining viability compared with EQ-5D-3L. At the beginning of this study, only the Japanese version of EQ-5D-3L was available, but since EQ-5D-5L became available during the study period, both EQ-5D-3L and EQ-5D-5L were administered to the 20 participants in the latter period. The results showed that EQ-5D-3L revealed no improvement, whereas EQ-5D-5L showed significant improvement. These results suggest that if EQ-5D-5L had been used from the beginning, significant improvement may have been observed.

FFMQ showed significant improvement. FFMQ is based on five factors that represent elements of mindfulness. Finding improvement with this scale means that participants are able to consider their own minds nonjudgmentally. This may have prevented them from ruminating, which occurs when an individual feels anxiety and makes him/her feel worse, and consequently improved STAI scores.

On the other hand, it should be noted that this study had several limitations. The first limitation was the use of a waiting-list as a control group; studies using a waiting-list reportedly have the potential to overestimate treatment effects 5). This is because participants assigned to the waiting-list are less likely to make changes on their own than those assigned to other control groups. Therefore, the effects of MBCT reported here may be overestimated. A second limitation was that the control group was not an active placebo group. It is well-known that "nonspecific factors" such as group sessions can positively influence clinical outcomes. However, given the importance of the practical rather than scientific perspective of this study, the authors believe that examining the differences

in outcomes between the standard care group and group to which MBCT was added should have been a higher priority than comparing MBCT and active placebo. A third limitation relates to the self-reported measurements. All measurements used in this study were the self-reported type. As a result, there is a possibility of reporting bias, such as participants adjusting their responses to meet the researcher's expectations. There were some contradictions in previous studies regarding the challenges of using self-reported measurement. For example, Rush, A. J. et al.18) reported a marked correlation between self-reported and clinician-rated measurements in a sample of depressed patients. On the other hand, Dunlop, B. W. et al.7) claimed that self-reported measurement did not correlate well with clinicians' ratings. These contradictory results may confound the interpretation of self-reported outcomes. However, Dunlop et al. also noted that the correlation between self-reported and clinician-rated measurements become stronger over time. Given that the average duration of treatment for the participants in this study was almost 10 years, the effect of using self-reported outcomes was not considered significant. Future studies should take these limitations into account when considering study designs.

To the best of our knowledge, this research report 16) is the first English-language paper on a mindfulness RCT in Japan. As indicated by the title of the paper, we believe that this is also the first study in the world to conduct intervention for anxiety disorders in a secondary-care setting. In other countries, family physicians in the community often examine patients with psychiatric disorders as part of primary care. As a result, in RCTs of other anxiety disorders, research interventions are often conducted in primary care settings, and less than half of patients receiving pharmacotherapy are likely to have received a mindfulness program early in their treatment. In Japan, however, most participants were already receiving pharmacological intervention because they had been seen by a specialist from the start. We believe that the significant efficacy seen in this study in these patients points to the possibility of new treatment options for many patients who either do not respond adequately to pharmacotherapy or cannot discontinue their medications despite some degree of efficacy. Once a patient has been diagnosed, it is difficult to achieve complete remission of anxiety disorders. It would be a great source of pleasure if the results of this study could help to build evidence for the therapeutic effects of mindfulness, enabling it to

become a treatment option for many patients suffering from anxiety disorders.

As a side story, when I conceived of this intervention study in 2013, not many RCTs of mindfulness for anxiety disorders (especially for MBCT) had been published, and I thought that a RCT for anxiety disorders alone would be meaningful. However, since around 2015, a number of RCTs have been published, and I was sometimes concerned that the novelty of this study had been lost. I keenly realized the importance of promptly conducting research and publishing papers when conducting research in a field where research is flourishing worldwide.

Conclusion

While the effects of mindfulness-based interventions on various diseases have been verified in other countries, they have not been fully verified in Japan, and it is not clear whether the same effects can be confirmed in Japanese patients. Scientific support is essential for mindfulness to spread appropriately. In Japan, it is hoped that high-quality scientific research will further validate mindfulness in the future.

In addition to RCT of mindfulness for anxiety disorders, the research team at Keio University School of Medicine has already completed RCTs of mindfulness for breast cancer patients, healthy people, and healthcare professionals. We are currently conducting another RCT focusing on long-term effects. The reason for this is that while many studies examined short-term effects, specifically the standard two-month immediate post-intervention period, the long-term effects, such as six months to one year after the intervention, have not yet been fully examined. We are examining differences in the long-term effects of MBCT by dividing patients into two groups: 2-month program plus monthly follow-up program for 10 months in one group, and no follow-up program in the other group, with an eye toward what methods might be appropriate to ensure that the effects of MBCT are sustained long-term.

Thus, our current focus is mainly on RCTs, but research on mechanisms of effectiveness is equally important, such as why mindfulness works. This is because clarification of this issue will help to clarify the direction of programs that are more effective and sustainable long-term. Segal, one of the developers of MBCT, has published a paper focusing on the mechanisms of mindfulness in addition to numerous RCTs. More research in these areas will be needed in order to make MBCT more effective, efficient, and long-lasting in the future.

There are no conflicts of interest to

disclose in connection with this paper.

This paper is a rewrite in Japanese by one of the authors of a recent research article16) published in PCN, with additions on the significance and perspectives of the article at the request of the Editorial Board of Psychiatria et Neurologia Japonica.

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表 1　研究対象者の特性

Characteristics	Total (n = 40)	MBCT (n = 20)	Control (n = 20)	Statistics
Age（years）	41.4 ± 10.0	42.9 ± 8.3	39.8 ± 11.4	$P = 0.33^a$
Sex（female）	15（37.5%）	6（30%）	9（45%）	$P = 0.33^b$
Duration of anxiety disorders from the onset（months）	151.2 ± 123.3	157.5 ± 125.9	144.9 ± 123.6	$P = 0.75^a$
Treatment（months）	110.7 ± 118.7	112.3 ± 127.1	109.1 ± 113.1	$P = 0.93^a$
Diagnosis				$P = 0.33^b$
Panic disorder/agoraphobia	15（37.5%）	9（45%）	6（30%）	
Social anxiety disorder	25（62.5%）	11（55%）	14（70%）	
Clinical measures				
STAI-state	49.0 ± 10.9	47.9 ± 9.6	50.1 ± 12.2	$P = 053^a$
STAI-trait	55.8 ± 11.8	54.1 ± 12.1	57.6 ± 11.5	$P = 0.35^a$
K6	9.2 ± 4.8	8.2 ± 4.5	10.1 ± 5.0	$P = 0.21^a$
CES-D	21.9 ± 11.7	18.5 ± 12.0	25.4 ± 10.5	$P = 0.06^a$
FFMQ（total）	105.6 ± 2.8	107.8 ± 3.3	103.5 ± 4.6	$P = 0.45^a$
EQ-5D（-3L）	0.80 ± 0.18	0.81 ± 0.18	0.78 ± 0.18	$P = 0.57^a$
SF-12-PCS	55.0 ± 10.2	53.5 ± 10.9	56.4 ± 9.6	$P = 0.38^a$
SF-12-MCS	46.7 ± 8.1	47.3 ± 8.5	46.2 ± 7.9	$P = 0.67^a$
Medication				
psychotropic drug	38（95%）	18（90%）	20（100%）	$P = 0.17^b$
Antidepressant	27（67.5%）	11（55%）	16（80%）	$P = 0.09^b$
disease specific measures	Total（n = 14）[c]	MBCT（n = 9）	Control（n = 5）	Statistics
MIA	1.9 ± 0.5	1.8 ± 0.6	2.1 ± 0.6	$P = 0.22^a$
	Total（n = 25）	MBCT（n = 11）	Control (n = 14)	Statistics
LSAS	77.6 ± 26.2	74.5 ± 29.5	80.0 ± 24.1	$P = 0.61^a$

Data are n（%）or mean ± SD
[a] Student's t-test
[b] Chi-square test
[c] Total number decreased because of missing value
（文献 16 より引用）

Table 1 Characteristics of Study Subjects
(Adapted from Ref. 16.)

表 2　混合効果モデル反復測定法による解析結果（ITT 解析）

Clinical measures	Weeks	MBCT (n＝20)	Control (n＝20)	Comparison	
		Mean（SD）	Mean（SD）	Difference in mean change scores†§ (95% CI)	*P* value
Primary outcome					
STAI-state	0 (baseline)	47.9 (9.6)	50.1 (12.2)	—	—
	4	45.7 (13.9)	52.1 (8.6)	−4.0 (−10.9 to 2.9)	0.25
	8	37.2 (12.2)	49.5 (10.3)	−10.1 (−16.9 to −3.2)	0.004
STAI-trait	0 (baseline)	54.1 (12.1)	57.6 (11.5)	—	—
	4	50.4 (13.4)	57.3 (10.6)	−3.5 (−8.9 to 1.8)	0.19
	8	42.5 (11.0)	57.6 (11.5)	−11.7 (−17.0 to −6.4)	<0.001
Secondary outcome					
K6	0 (baseline)	8.2 (4.5)	10.1 (5.0)	—	—
	4	6.8 (5.5)	11.2 (5.5)	−2.6 (−5.4 to 0.2)	0.07
	8	3.8 (3.1)	10.4 (5.0)	−4.7 (−7.5 to −0.9)	0.001
CES-D	0 (baseline)	18.5 (12.0)	25.4 (10.5)	—	—
	4	16.2 (12.1)	24.1 (11.9)	−0.20 (−6.6 to 6.2)	0.95
	8	12.6 (7.6)	23.6 (9.8)	−2.99 (−9.4 to 3.4)	0.36
FFMQ（total）	0 (baseline)	107.8 (14.3)	103.5 (20.6)	—	—
	4	113.6 (18.7)	100.7 (19.0)	6.86 (−1.8 to 15.5)	0.12
	8	119.2 (17.5)	100.1 (18.8)	13.93 (5.2 to 22.7)	0.002
EQ-5D-3L	0 (baseline)	0.81 (0.18)	0.78 (0.18)	—	—
	4	0.81 (0.18)	0.75 (0.18)	−0.51 (−3.0 to 2.0)	0.68
	8	0.85 (0.19)	0.77 (0.18)	−0.36 (−2.8 to 2.1)	0.77
SF-12-PCS	0 (baseline)	53.5 (10.9)	56.4 (9.6)	—	—
	4	53.1 (10.3)	55.0 (14.9)	1.23 (−6.2 to 8.7)	0.75
	8	55.3 (8.1)	48.9 (13.8)	8.57 (0.9 to 16.2)	0.03
SF-12-MCS	0 (baseline)	47.3 (8.5)	46.1 (7.9)	—	—
	4	46.5 (10.0)	45.7 (10.6)	−0.78 (−7.1 to 5.6)	0.81
	8	49.7 (9.5)	47.6 (13.6)	1.54 (−5.0 to 8.1)	0.64

† Difference in mean change scores are between-group difference in least squares mean treatment change scores from baseline to data point from mixed-effects model for repeated measurement analysis
§ Between-group difference is MCBT group minus Control group
（文献 16 より引用）

Table 2 Summary of analysis of repeated-measure analyses (intent-to-treat population)
(Adapted from Ref. 16.)