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MINDFULNESS BASED COGNITIVE THERAPY VERSUS GROUP PSYCHO-EDUCATION FOR PEOPLE WITH GENERALIZED ANXIETY DISORDER: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Research suggests that a course of eight-week mindfulness based cognitive therapy (MBCT) may be effective in the treatment of generalized anxiety disorder (GAD) although few randomized controlled studies have been conducted.
Aims: To compare changes in anxiety and worry levels among participants with GAD randomly assigned to MBCT, psycho-education (PEG) using cognitive behavioural therapy principles and usual care (UC).
Methods: One hundred and eighty-two participants with GAD were recruited. Both the MBCT and PEG received 8 week intervention while the control group received usual care and were followed over 5 months after baseline assessment (3 months post intervention). The MBCT and PEG were further followed for additional 6 months. Primary outcomes were anxiety and worry levels while secondary outcomes included depressive symptoms, quality of life and level of mindfulness.
Results: Linear mixed models demonstrated significant group-time interaction ($F(4, 148) = 5.10$, $p = 0.001$) effects for decrease in anxiety measured by BAI for both MBCT and PEG participants relative to UC. Significant group-time interaction effect was observed in worry symptoms, depressive symptoms and mental health related quality of life for PEG only although both MBCT and PEG improved in level of mindfulness. At eight and eleven months, no significant difference in outcome measures were observed between PEG and MBCT although the study was not powered as an equivalence trial to compare PEG and MBCT.
Conclusion: These results suggest that although both MBCT and PEG appear to be superior to usual care for the reduction of anxiety symptoms, although PEG has the additional benefits of reducing worry and depressive symptoms among people with GAD.

Trial registration number: CUHK_CCT00267

Introduction

Generalized anxiety disorder (GAD) is a chronic psychiatric disorder characterized by pervasive, persistent and uncontrollable worry.[1] It is associated with significant functional impairment,[2] morbidity and health care utilizations.[3] Although cognitive behavioral therapy has been shown to be effective for treating GAD,[4] not all treated are able to achieve high functioning after treatment.[5] Moreover, there is often a shortage of CBT therapists and individual therapeutic approach can be expensive in health care systems with limited resource.[6] This calls for the evaluation of other potential treatments such as group intervention which may be more cost-effective.

Mindfulness based interventions have been used and studied for a variety of physical and psychological conditions.[7-11] Mindfulness based cognitive therapy (MBCT), a psychological intervention developed by clinical psychologists based on mindfulness based stress reduction with integration of cognitive behavioral elements, has been shown to be effective in reducing relapse among people who suffer from recurrent episodes of major depression[11-13] and is now being incorporated into guidelines of the British body, the National Institute for Health and Care Excellence (NICE) as a treatment option for those who suffer from recurrent depression.[12-14] Most studies that evaluated the effectiveness of MBCT have been conducted among patients with recurrent depression. Only limited studies have been conducted to evaluate the effects of MBCT in reducing anxiety and worry among people who suffer from GAD. Moreover, these studies have been limited by their study design such as not having control group for comparison,[15-18] having a small sample size[15-19] or no randomization[19]. Mindfulness based stress reduction (MBSR), without the cognitive components, have also been investigated previously[20, 21] and recently,[22] a randomized controlled trial comparing MBSR with an active control has shown promising results on the reduction of clinically relevant anxiety symptoms among patients with GAD. To our knowledge,

the current study is one of the few studies that had included an active comparison group to evaluate the effectiveness of MBCT in reducing anxiety and worry symptoms among patients with generalized anxiety disorder recruited from primary care and the community. We hypothesized that participants in the MBCT group would be better than a psycho-education control group using CBT principles (PEG) and also the usual care control in reducing anxiety symptoms in this population. We included PEG as a comparison group was for pragmatic reason since psycho-education group using CBT principles has been suggested as a low intensity intervention for people with GAD in primary care.[23]

Methods

The protocol of this study has been published previously[24] although the follow up assessment for the usual care group ended at 5 months after baseline assessment due to changes in service provision in the local area (before the trial started, there was a waiting time of 9 to 12 months for a patient to be seen by psychiatrist or psychologist in public clinics which was reduced to six months during the trial with a new service program). In brief, this randomized controlled study included three study arms. These included a mindfulness based cognitive therapy (MBCT) group led by trained instructors, a psycho-education group (PEG) using CBT principles led by clinical psychologists, and a usual care control group (UC) whose participants were offered MBCT at the end of the 5 months after baseline assessment. Self-reported assessments were administered at similar time points, including baseline, 2 months after baseline assessment (immediately post intervention for the treatment arms) and at 5 months after baseline assessment for all three arms. Both the MBCT and PEG group were further followed-up at 8 and 11 months after baseline assessment while the UC group was only followed up to 5 months after baseline assessment. All data were entered and analysed using the software PASW Statistics 18. The study was approved by the Clinical Research

Ethics Committee (CREC) of the Joint Chinese University of Hong Kong – New Territories East Cluster. The CREC reference number is CRE-2009.353-T.

Participants

All participants were recruited from: 1) advertisements with study information being seen in health education columns of local newspapers; 2) public general practice or family medicine clinics (GPs); 3) non-governmental organizations and community centres that cater for people with chronic conditions**..**

All recruited participants fulfilled the following criteria: 1) aged 21-65; 2) having a DSM-IV principal diagnosis of generalized anxiety disorder on a Structured Clinical Interview for DSM-IV (SCID) and a score of 19 or above using the Chinese version of the Beck Anxiety Inventory at baseline;[25-26] 3) could understand Cantonese; 4) were willing to attend either the MBCT or PEG group sessions; 5) if they were on medications for anxiety, they should have had been on stable doses of medication for at least 2 months before starting the intervention. Participants were excluded if they: 1) were illiterate as they would have been unable to complete the self-report assessment; 2) were having psychiatric and medical co-morbidities that were potentially life threatening (i.e. psychosis, suicidal ideation, terminal medical illness) or those expected to severely limit patient participation or adherence (e.g. psychosis, current substance abuse, dementia, pregnancy); 3) were currently seeing a cognitive behavioural therapist or psychotherapists/counsellors for any psychological problems; and 4) have had or had regular meditation or yoga practice.

All interested participants were screened initially over the phone using these inclusion and exclusion criteria by trained research assistants with a graduate degree in psychology or public health. Those initially screened and were deemed eligible were then scheduled a diagnostic

interview with the principal investigator (PI) to further confirm eligibility using the Structured Clinical Interview for DSM-IV (SCID) and a structured questionnaire. They were screened for common psychiatric disorders (major depression, somatic symptoms, alcohol dependence and panic disorder) in primary care using the Primary Health Questionnaire (PHQ).[27] Among participants who were screened positive for the GAD schedule of the PHQ, the Structured Clinical Interview for DSM-IV (SCID) was further conducted to confirm the GAD diagnosis by the PI. Participants were then informed about their eligibility for the study and were further contacted according to the programme schedule once it was available. Written informed consents were obtained from all participants before taking part in this study and both the PI and the research assistant were trained to use the DSM-IV (SCID) by a psychiatrist. Following the diagnostic interview, simple randomization method was used to randomly assign eligible participants into one of the three groups using the Microsoft Excel RAND function. For every batch of participants recruited, one third of the participants were randomized to the MBCT group, one third to the PEG group and the rest to the control group. To ensure concealment of randomization, a biostatistician who is not part of this study pre-generated random numbers from a normal distribution. Participants were ranked in order according to their generated values. Participants ranked in the top one third of the list were assigned to group A, the middle third to group B, and the remaining to group C, where A, B, and C represents the treatment patient will receive (e.g., A=MBCT, B=PEG, C=control) and only the research coordinator could decode it. The timing and venue of the classes for the two groups were arranged suitably to avoid interaction and exchange of information between participants of the two groups.

Interventions

Mindfulness Based Cognitive Therapy (MBCT): Five MBCT groups were led by two clinical

psychologists and one social worker who were all experienced in leading MBCT group. All of them had received intensive MBCT and MBSR training retreats and had both practiced and conducted mindfulness based cognitive therapy for patients for at least 2 years. The intervention consisted of eight weekly 2-hour sessions involving up to 15 participants. Our intervention programme followed the Mindfulness-based Cognitive Therapy for Depression protocol published in the book by Segal, William and Teasdale.[12] Modifications were made by a team of MBCT instructors in order to make the intervention more suitable for people with anxiety disorders with the cognitive behavioral components dealing with depression being replaced by components dealing with anxiety. This included discussing the cognitive behavioural model of GAD in session 2, automatic anxiety thoughts in session 4, reactive-avoidance and ruminative worrying in session 5, and the development of an action plan in line with personal value, and relapse prevention of anxiety in session 7.

The session summary is attached as the Appendix 1. During the intervention period, participants in this group were given daily homework exercises including guided awareness exercises by CDs, which included sitting meditation, body scan, mindful movements. Moreover, shorter unguided awareness exercises such as the three-minute breathing space were also included in the homework to aim at increasing moment by moment awareness of feelings, thoughts and bodily sensations together with exercises designed to integrate the application of mindfulness skills into daily activities. All sessions were audio-taped with a subset reviewed to ensure the fidelity of the programme. All participants were instructed to practice mindfulness meditation daily for 45 minutes a day.

Psycho-education group (PEG) based on cognitive behavioural therapy principles: The PEG was designed to be comparable to MBCT in terms of the course structure and the therapist's contact

time and attention, with participants needed to comply with an agenda during each session with a similar amount of homework assignments to that of the MBCT group. The PEG consisted of eight weekly 2-hour sessions with didactic teaching and minimal group interaction and discussion and the content of the teaching was based on White's book on Treating Anxiety and Stress, a handbook that is used by clinical psychologists to help people cope with anxiety using the cognitive behavioral approach.[28] The brief description of the schedule of PEG is presented in Appendix 2. The topics included preparing for stress control, learning about stress, controlling one's body, thoughts and action; controlling one's panic, insomnia, depression and future. In addition to the didactic teaching content, simple relaxation skills such as muscle relaxation skills were also taught during class although instructors have been asked, as best as they could, not to teach any skills in a way that may enhance mindfulness. Two clinical psychologists with at least 2 year experience in cognitive behavior therapy practice or teaching were employed to lead the PEG groups.

Usual Care Control group (UC): Participants in the usual care control group did not receive any specific intervention but they are allowed unrestricted access to primary care services. In Hong Kong, the average consultation time for public primary care clinics is about 6 minutes and it is often difficult for doctors to have enough time to deal with patients' emotional problems. The waiting time for referral to be seen by mental health service specialists is at least 6 months.

Outcome Measures

Participants' demographic information including age, sex, marital status, education levels, monthly income, religious belief and number of family members were also collected at baseline. All outcome measures and details of health service utilizations were collected at similar time points (baseline, 2 months after baseline assessment, and at 5 months after baseline assessment) for all three groups. Participants randomized to either the MBCT or PEG group were further followed for 6 and 9

months (8 months and 11 months after baseline assessment) and both primary and secondary outcome measures were assessed at these two time points.

The primary outcome measures were clinically relevant anxiety symptoms measured by the Chinese version of Beck Anxiety Inventory and worry symptoms measured by the Penn State Worry Questionnaire (PSWQ) five months after baseline assessment (3 months post intervention).[29-32] Secondary outcome measures included : clinically relevant depressive symptoms measured by the validated Chinese version of the Center for Epidemiologic Studies Depression Scale (CES-D) with the cut-off point of 16 being used to indicate "significant" depressive symptoms;[33] the validated Chinese version of the Medical Outcomes Study Short-Form Health Survey (SF-12) which reported health-related quality of life;[34] the Chinese version Five Facet Mindfulness Questionnaire (FFMQ).[35-36] Both primary and secondary outcome measures were collected at baseline, 2, 5, 8 and 11 months after baseline assessment.

Statistical analysis

To investigate significant changes over time, linear mixed models (LMM) were conducted for both primary and secondary outcomes following the intention to treat principle. A two-sided P value of 0.05 or less will be considered as statistically significant. The use of linear mixed models provided the means to include subjects with incomplete data (missed 1 or 2 questionnaires) to assess the treatment effect over time (i.e. trend or group-time interaction). In our models, intervention group, time, and the interactions between the intervention group and time were treated as fixed factors, while an unstructured covariance structure was employed. Statistical analysis of the primary and secondary outcome measures, including BAI, PSWQ, CES-D, SF-12, FFMQ, as well as health service utilization over time were made. In addition, to account for differences in treatment effect as a result of difference in compliance among treatment groups, complier adjusted causal effect

(CACE) analysis was conducted according to the causal framework and estimation approaches described previously.[37-39] The outcome was the change of BAI score from baseline to 5-months after baseline assessment. We defined CACE as the difference in mean BAI score change between the compliers in the treatment group and the compliers in the control group. Participants were defined as compliers if they have complied with at least 80% of classes (i.e., ≥7 classes attendance), a commonly used cut-off.[40-41] Treatment specific (MBCT/PEG) CACE was estimated. Standard errors were obtained by bootstrapping technique.[37] The CACE analysis was conducted using R, all other analyses were conducted in PASW Statistics 18.

Sample size calculation

At the time of trial, no studies have compared MBCT with an active control for people with GAD, the research findings from a study that compared CBT with an education group were used for sample size calculation.[42] Assuming a common SD of 7.4 and the average mean change of a BAI score at post intervention for patients in the MBCT group was 5.6, in the PEG group was 2.0 and that in the UC group was 1.1 with a type I error of 5% and 80% power to detect statistically significant differences between the MBCT and PEG group, as well as MBCT and UC group, the required sample size was 53 participants per group. With a presumed dropout rate of 30%, we aimed to recruit 76 participants per group.

Results

One thousand two hundred and nine potential participants were screened by telephone for eligibility. Among these, 263 participants with anxiety symptoms were scheduled for diagnostic interviews and to confirm their eligibility with the PI. In the end, 182 participants who met the inclusion criteria were randomized. Two participants from the MBCT group and one from the PEG group dropped out before the start of the intervention due to time constraints. Four participants who

were not happy with the randomization results quit the usual care control group immediately without returning the baseline questionnaires. Details of the recruitment process were shown in the flow diagram (Figure 1).

The mean age of our sample was 50 (SD = 10) years. The majority of our participants were females (79%). The demographic characteristics of our participants are presented in Table 1. All participants scored more than 16 (the cut-off threshold for having clinically relevant depressive symptoms) on CES-D and thus were co-morbid with depressive symptoms. Sixty-three (35%) participants were already on more than 2 months of regular medication for treating GAD and/or depressive symptoms with 26 people in the MBCT (42.6%) ; 14 in the PEG (23.0%) and 21 in the UC (35.0%).

The mean class attendance for MBCT class was 6.4 (SD =1.9) sessions and that of the PEG was 7.1 (SD=1.5) classes. Forty-three (71%) participants of MBCT attended six or more sessions and 24 of whom (39%) attended all eight sessions while fifty four (89%) participants attended six or more sessions and more than half (56%) completed all eight psycho-education sessions for the PEG. No significant differences were observed on baseline outcome measures between the completers and the non-completers.

Effects on primary outcome measures

BAI scores in both the MBCT and PEG groups decreased significantly at 2 and 5 months after baseline assessment with no change observed for the UC group. The estimated means and 95% confidence intervals (C.I.) as generated by the LMM procedure were used to produce trajectories in Figure 2. At 2 and 5 months after baseline assessment, a significant relative change of score was revealed between MBCT vs. UC and PEG vs. UC (Table 2). No differences were found in BAI scores between the MBCT and PEG groups at any time point. Overall, LMM demonstrated a

significant group-time interaction ($F(4, 148) = 5.10$, $p = 0.001$).

For the PSWQ scores in the MBCT, PEG and UC, the estimated means and 95% confidence intervals (C.I.) as generated by the LMM procedure were used to produce trajectories in Figure 2. At 5 months after baseline assessment but not at 2 months after the baseline assessment, a significant relative change of score was revealed between PEG vs. UC but not for MBCT vs. UC or MBCT vs. PEG (Table 2).

As stated previously, participants in the UC group were followed only up to 5 months after baseline assessment. Thus, follow up data at 8 and 11 months after baseline assessment were only available for the MBCT and the PEG groups. Both BAI and PSWQ scores continued to decrease significantly within the MBCT and PEG groups at 8 and 11 months after baseline assessment (i.e., significant time effect) but there were no significant group differences between the PEG and MBCT groups at these two time points (Figure 2).

Effects on secondary outcome measures

Statistical analysis showed a significant group -time interaction (CES-D: $F(4,154) = 3.6$, $p = 0.08$; MCS12: $F(4, 147) = 4.5$, $p = 0.002$) in CES-D and MCS12. As shown in Figures 3b and 3d, significant improvements over time were observed only within the PEG group on CES-D and MCS12. Significant group differences were seen on these two scales between PEG and UC groups at 2 and 5 months after baseline assessment. However, no significant group differences were observed between the MBCT and UC groups or the MBCT and PEG group at these time points. Moreover, there was no significant group difference in these outcomes between MBCT and PEG group at 8 and 11 months.

In terms of mindfulness, group-time interaction ($F(4, 148) = 3.6$, $p = 0.008$) was reported for FFMQ. Scores of FFMQ in both MBCT and PEG groups increased significantly at 2 and 5 months

after baseline assessment (Figure 3e). The significant change of scores was also reported for MBCT vs. UC and PEG vs. UC at 2 and 5 months after baseline assessment. No group difference was observed between the MBCT and PEG groups.

Based on the 8 and 11 months after baseline assessment result, both groups showed significant improvements on CES-D, PCS12, MCS12 and FFMQ scores, however there was no statistically significant difference between the two groups. (Figure 3)

The differences of medical visits made per month were only observed at 5 month after baseline assessment between the PEG and the UC group (p =0.025), but not between MBCT vs. PEG groups or between MBCT vs. UC groups.

CACE analysis

There was no statistically significant difference of class attendance between the two intervention groups (Appendix 3, Fisher exact test p-values = 0.2147) or when we dichotomised patients to complier or non-compliers (chi-square test p-value = 0.074). In addition, no baseline covariate is shown to be significantly associated with the complier status. The CACE estimates obtained for MBCT and PEG were -8.56 (SE 3.85) and -8.73 (SE 2.41).

Discussion

The aim of the current study was to test the effects of MBCT in treating patients with GAD when compared with a psycho-education group using CBT principles and a usual care control group in a primary care setting. Our study is the first that has compared MBCT with a low intensity structured evidence based intervention[23] and a usual care control group. We have initially hypothesized that MBCT would be better than both PEG and UC in the reduction of anxiety and worry symptoms and this hypothesis was not supported.

Our results showed that both MBCT and PEG were better than UC in the reduction of anxiety

among people with GAD and PEG was better than UC group in helping people reduce worry symptoms although only at 5 months after baseline assessment. There was no statistically significant difference in primary outcomes between PEG and MBCT and we are unable to tell whether the lack of difference observed between the MBCT and PEG group was statistically significant as the study was not powered to test for equivalence between the two interventions. However, the differences in outcomes between the MBCT and PEG group appear to be quite small and it is likely of limited clinical significance. We also show that PEG may have the additional beneficial effects on the reduction of depressive symptoms and improvement of mental health related quality of life. .

We are uncertain about the reasons for the superior effects of PEG on worry and depressive symptoms, mental health related quality of life as well as the higher attendance of partcipants in the PEG. We can speculate that culture specific effects may have affected treatment expectancy among patients for treatment efficacy. Although Hong Kong is a city and part of Asia with a long tradition of meditation practice (e.g. in Buddhism), the format and teaching of PEG may be seen as a more scientific and modern Western approach when compared to that of MBCT which the majority of content is based on the teaching of meditation and can be perceived as similar to an ancient religious practice.

Although there are a lack of studies evaluating the efficacy of MBCT on reducing anxiety symptoms among people with GAD or comparing MBCT to a group psychoeducation based on CBT principles, Koszycki and colleagues have compared the efficacy of 8-week mindfulness based stress reduction, not MBCT, with a 12 week group cognitve behavioral therapy among patients with social anxiety disorder (not GAD).[43] They showed that although patients in both treatment groups improved in terms of anxiety symptoms, patients receiving the group CBT had signficantly larger

reduction in their anxiety symptom scores although the two interventions were similar in improving other aspects of mood, functionality and quality of life. More recently, Hoge et al[22] have conducted a randomized controlled trial evaluating the effects of MBSR, not MBCT, on anxiety and stress reactivity among people with GAD among 93 participants. They showed that MBSR was superior to an active control consisting of stress management didactic heatlh education in reducing anxiety measured by both the BAI and Clinical Global Impressions Scales. However, we must be cautious when compared these findings with those of our studies since we have employed a different comparison group. We have used a didactic psychoeducation group using CBT principles plus relaxation skills training instead of a group CBT treatment as described by Koszycki et al[43] (assumed to be of higher intensity due to its group treatment nature) or a simple didactic presentations on stress management (assumed to have lower intensity since no CBT principles were introduced) as described by Hoge et al[22]. The lack of observed superiority of MBSR to psychoeducation as was shown in Hoge et al[15] thus may have been due to the fact that our PEG may produce more therapeutic effects than the simple use of stress management education. Moreover, we have also included simple relaxation skills which may have added additional therapeutic effects. These differences in findings thus may make sense if we take our PEG group as a psychological intervention with lower intensity than that of a group CBT treatment but of higher intensity than that of a stress management health education.

Another unexpected findings of this study is that both the MBCT and PEG groups have improvements on "mindfulness" as measured by the FFMQ. Although studies have been conducted to validate a number of scales to measure mindfulness, findings have been inconsistent[44]. The current findings suggest that either the FFMQ is indeed not sensitive enough to measure the construct of mindfulness or that people who were randomized to the PEG group did experience

change in their awareness or mindfulness as a result of the psychoeducation received although the question of whether mindfulness can be measured using questionnaires remains. Furthermore, the main effect of group and time remained significant after adjusting for the FFMQ suggests that FFMQ may not be a sensitive enough instrument to measure the positive changes associated with participation in mindfulness intervention (results not shown).

There are a number of limitations in our current study. First, the participants in the MBCT group had a much lower adherence than those who were randomized to the PEG group. The mean number of sessions attended by participants randomized to the MBCT group was fewer than those randomized to the PEG group. As a result, the attrition rate might have contributed to the smaller improvement on the other measured outcomes when compared to the participants randomized to the PEG group although our CACE analysis did not demonstrate any significant difference in outcomes due to compliance effect.

In this study, we initially targeted to recruit 228 participants with a presumed drop out rate of 30% (159 particiapnts) and we ended up recruited 178 participants with 4 participants (4%) dropped out of the study without any baseline data. At the end of intervention, 55 (90%), 54 (89%) and 48 (86%) questionnaires were collected in MBCT, PEG and UC group respectively and a lower proportion of questionnaires were collected at the later time points. To account for the missing data due to non-returned or incomplete questionnaires, we have used linear mixed model and have followed the intention to treat principle but the findings could have been affected by the incomplete data.

Second, our outcome measures were based on self-reported questionnaires collected at similar time points. Although all scales used in this study were validated, no clinician rated instruments or diagnostic interviews at follow up were used. As a result, we did not know if the improvement in

these anxiety symptoms have led to clinical remission of GAD.

Third, due to ethical reasons, we were only able to compare the two interventions (MBCT and PEG) with the usual care control group up to three months as it was unethical not to initiate treatment among these participants when the waiting time for psychiatric servcies was reduced. As a result, long term findings were only available for the two comparison groups.

Fourth, we have included participants who at the time of recruitment, suffered from at least moderate levels of generalized anxiety symtpoms, based on validated self reported questionnaires and the majority of participants were recruited via adverstisement. As a result, we cannot generalize our results to patients who suffer from a milder degree of anxiety symptoms and also to all patients in actual clinical settings and there may have been a selection bias of recruited participants being more motivated when compared to those of clinic patients in our study.

Fifth, due to the design of our study, we are unable to know whether differences between both MBCT and PEG and UC at 5 months were simply due to differences in attention/time offered to participants rather than specific effects about the content of either therapeutic modality although there is established evidence that supports the effectiveness of PEG for reducing anxiety symptoms.

Finally, we had two primary outcome measures and two comparisons in this study which could have caused a type I error due to multiple testing. However, our findings on performing Bonferroni correction (results not shown) show that the effects of interventions on primary outcomes after correction remain largely the same.

Conclusion

This randomized controlled clinical trial showed that although participants from both MBCT and PEG groups had a significant decrease in anxiety symptoms as compared to the usual care control group, PEG appears to have higher acceptability and better effects on worry sympotms and

reduction of depressive symptoms among patients with GAD in this population. Future studies can also be conducted to explore if there are specific patient popuations or unique patient characteristics who may be more suitable for either MBCT or group psychoeducation using CBT principles. With this respect, recent research has suggested that anxiety sensitivity [45] or stress reactivity[15] may differentially moderate treatment outcomes in CBT and adapted MBSR for anxiety disorders.[45]

Declaration of interest

None

Reference

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders,* Fourth Edition. Washington, DC; American Psychiatric Association, 1994.

2. Kessler RC, Walters EE, Wittchen HU. Epidemiology. In *Generalized Anxiety Disorder: Advances in Research and Practice* (ed RG Heimberg, CK Turk, DS Mennin): 29-50. New York: Guilford Press; 2004.

3. Greenberg PE, Sisitsky TK Kessler RC, Finkelstein SN, Berndt ER, Davidson JRT, et al. The economic burden of the anxiety disorders in the 1990s. *J Clin Psychiatry* 1999; **60**: 427-35.

4. Cuijpers P, Sijbrandij M, Koole S, Huibers M, Berking M, Andersson G. Psychological treatment of generalized anxiety disorder: a meta-analysis. *Clin Psychol Rev* 2014; **34**: 130-40.

5. Waters AM, Craske MG. Generalized anxiety disorder. In *Improving Outcomes and Preventive Relapse in Cognitive Behavioural Therapy* (ed MM Antony, DR Ledley, RG Heimberg): 77-127. New York: Guilford; 2005.

6. Sundquist J, Lilja A, Palmer Km Menon AA, Wang X, Johansson LM et al. Mindfulness group therapy in primary care patients with depression, anxiety and stress and adjustment disorders: randomized controlled trial. *B J Psychiatry* 2014; pii: bjp.bp.114.150243. [Epub ahead of print].

7. Kabat-Zinn J. *Full catastrophe living: using the wisdom of your body and mind to face stress, pain, and illness.* New York: Delacourt; 1990.

8. Chiesa A, Serretti A. Mindfulness-Based Interventions for Chronic Pain: A Systematic Review of the Evidence. *J Altern Complement Med* 2011, **17**: 83-93. doi:10.1089/acm.2009.0546.
9. Chiesa A, Serretti, A. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. *J. Altern. Compl. Medicine* 2009; **15**: 593–600.
10. Ledesma, D. and Kumano, H. Mindfulness based stress reduction and cancer: a meta-analysis. *Psycho-oncology* 2009; **18**: 571–9.
11. Fjorback LO, Arendt M, Ørnbøl E, Fink P, Walach H. Mindfulness-Based Stress Reduction and Mindfulness-Based Cognitive Therapy ? A systematic review of randomized controlled trials. *Acta Psychiatr.Scand.* 2011: **124**: 102-19.
12. Segal ZV, William JM, Teasdale JD. *Mindfulness-based cognitive therapy for depression. A new approach to preventing relapse.* New York: Guilford Press; 2002.
13. Chiesa A, Serretti A. Mindfulness based cognitive therapy for psychiatric disorders: A systematic review and meta-analysis. *Psychiatry Res* 2011; **187**: 441-453.
14. Williams JMG, Kuyken W. Mindfulness-based cognitive therapy: a promising new approach to preventing depressive relapse. *Br J Psychiatry*2012; **200**:359–360. doi: 10.1192/bjp.bp.111.104745

15. Evans S, Ferrando S, Findler M, Stowell C, Smart C, Haglin D. Mindfulness-based cognitive therapy for generalized anxiety disorder. *J Anxiety Disord* 2008; **22**: 716-721.
16. Craigie MA, Rees CS, Marsh A. Mindfulness-based cognitive therapy for generalized anxiety disorder: A preliminary evaluation. *Behav Cogn Psychoth* 2008; **36**: 553-68.
17. Yook K, Lee SH, Ryu M, Kim KH, Choi TK, Suh SY, et al. Usefulness of mindfulness-based cognitive therapy for treating insomnia in patients with anxiety disorder: A pilot study. *J Nerv Ment Dis* 2008; **196**: 501-3.
18. Vollestad J, Nielsen MB, Neilsen GH. Mindfulness and acceptance-based interventions for anxiety disorders: a systematic review and meta-analysis. *Br J Clin Psychol* 2012; **51**: 239-60.
19. Kim YW, Lee SH, Choi TK, Suh SY, Kim B, Kim CM, et al. Effectiveness of mindfulness-based cognitive therapy as an adjuvant to pharmacotherapy in patients with panic disorder or generalized anxiety disorder. *Depress Anxiety* 2009; **26**: 601-6.
20. Kabat-Zinn J, Massion AO, Kristeller J, Peterson LG, Fletcher KE, Pbert L, et al. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *Am J Psychiatry* 1992; **149** (7): 936-943.
21. Vøllestad J, Sivertsen B, Nielsen GH. Mindfulness based stress reduction for patient with anxiety disorders: evaluation in a randomized controlled trial. *Behav Res Ther* 2011; **49** (4): 281-288.
22. Hoge EA, Bui E, Marques L, Metcalf CA, Morris LK, Robinaugh DJ, et al. Randomized controlled trial of mindfulness meditation fore generalized anxiety disorder: effects on anxiety and stress reactivity. *J Clin Psychiatry* 2013; **74**: 786-792.
23. National Institute for Health and Clinical Excellence. *NICE clinical guidance 22 (amended). Anxiety (amended). Management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care*. April 2007. www.nice.org.uk/nicemedia/pdf/CG022NICEguidelineamended.pdf.
24. Wong SYS, Mak WWS, Cheung ELY, Ling CY, Lui WW, Tang WK, et al. A randomized, controlled clinical trial: the effect of mindfulness-based cognitive therapy on generalized anxiety disorder among Chinese community patients: protocol for a randomized trial. *BMC Psychiatry* 2011; **11**:187 doi:10.1186/1471-244X-11-187.
25. Kam IWK. *Development of the bilingual (Chinese/English) SCID-I (Structured Clinical Interview for DSM-IV Axis I disorder): a study of its reliability and validity in an in-patient population.* Dissertation for Part III Examination of Fellowship. Hong Kong: Hong Kong College of Psychiatrist; 2000.
26. Cheng SKW, Wong CS, Wong KC, Chong GS, Wong M, Chang SS, et al. A study of psychometric properties, normative scores, and factor structure of the Beck Anxiety Inventory – the Chinese version.

Chinese J Clin Psychol 2002; **10**: 4-6.

27. Spiter RL, Kroenke K, William JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999; **282**:1737-44.

28. White J: Treating Anxiety and Stress: *A group Psycho-educational approach using brief CBT.* Chichester: John Wiley & Sons, LTD; 2000.

29. Beck AT, Epstein N, Brown G, Steer RA. An Inventory for measuring clinical anxiety: Psychometric properties. *J Consult Clin Psychol* 1988; **56**:893-7.

30. Beck A T, Steer RA. *Beck Anxiety Inventory manual.* San Antonio: Psychological Corporation; 1990.

31. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. *Behav Res Ther* 1990; **28**: 487-95.

32. Zhong J, Wang C, Li J, Liu J. Penn State Worry Questionnaire: structure and psychometric properties of the Chinese version. *J Zhejiang Univ Sci B* 2009; **10**: 211-8.

33. Cheung CK, Bagley C. Validating an American scale in Hong Kong: The Centre of Epidemiological Studies depression scale (CES-D). *J Psychol* 1998; **132**: 169-86

34. Lam CLK, Tse EYY, Gandek B. Is the standard SF-12 health survey valid and equivalent for a Chinese population. *Qual Life Res* 2005; **14**: 539-47

35. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. *Assessment* 2006; **13**: 27-45.

36. Hou J, Wong SYS, Lo HHM, Mak WWS, Ma HSW. Validation of a Chinese Version of the Five Facet Mindfulness Questionnaire in Hong Kong and development of a short form. *Assessment* 2013; DOI: 10.1177/1073191113485121

37. Dunn G, Maracy M, Dowrick C, Ayuso-mateos JL, Dalgard OS, Page H et al. Estimating psychological treatment effects from a randomized controlled trial with both non-compliance and loss to follow-up. *Br J Psychiatry* 2003; **183**: 323-31.

38. Angrist JD, Imbens GW, Rubin DB. Identification of causal effects using instrumental variables (with discussion). *J AM Statist Assoc* 1996; **91**: 444-72.

39. Frangakis CE, Robin DB. Addressing complications of intention-to-treat analysis in the combined presence of all-or-none treatment-noncompliance and subsequent missing outcomes. *Biometrika* 1999; **86**: 365-79.

40. Hernán MA, Hernández-Díaz S.Beyongd the intention-to-treat in comparative effectiveness research. *Clin Trials* 2012; **9**: 48-55.

41. Dodd S, White IR, Williamson P. Nonadherence to treatment protocol in published randomized controlled trials: a review. *Trials* 2012; **13**: 84.

42. Wetherell JL, Gats M, Craske MG. Treatment of generalized anxiety disorder in older adults. *J Consult Clin Psychol* 2003; **71**: 31-40.

43. Koszycki D, Benger M, Shlik J, Bradwejn J. Randomzied trial of a meditation-based stress reduction program and cognitive behavior therapy in generalized social anxiety disorder. *Behav ResTher* 2007; **45**: 2518-2526.

44. Park T, Reilly-Spong M, Gross CR. Mindfulness: a systematic review of instruments to measure an emergent patient-reported outcome (PRO). *Qual Life Res* Published Online First: March 2013. doi 10.1007/s11136-013-0395-8

45. Arch JJ, Ayers CR. Which treatment worked better for whom? Moderators of group cognitive behavioral therapy versus adapted mindfulness based stress reduction for anxiety disorders. *Behav Res Ther* 2013; **51**: 434-42.

Table 1 Demographic characteristic of participants

	Total (n=182)	**MBCT (n=61)**	**PEG (n=61)**	**UC (n=60)**
Age (Mean ± SD)	50.00 ± 10.02	50.40 ± 9.95	50.79 ± 9.57	48.78 ± 10.59
Gender				
Female	144 (79.1%)	48 (78.7%)	48 (78.7%)	48 (80.0%)
Male	38 (20.9%)	13 (21.3%)	13 (21.3%)	12 (20.0%)
Education				
Primary	28 (15.7%)	10 (16.9%)	7 (11.7%)	11 (18.6%)
Secondary	90 (50.6%)	31 (52.5%)	31 (51.7%)	28 (47.5%)
Diploma	21 (11.8%)	9 (15.3%)	6 (10.0%)	6 (10.2%)
Degree or above	39 (21.9%)	9 (15.3%)	16 (26.7%)	14 (23.7%)
Employment				
Unemployed/housewife/retired	100 (57.8%)	34 (58.6%)	33 (55.9%)	33 (58.9%)
Employed	73 (42.2%)	24 (41.4%)	26 (44.1%)	23 (41.1%)
Marital Status				
Married	129 (71.7%)	38 (63.3%)	48 (80.0%)	43 (71.7%)
Single/Separated	51 (28.3%)	22 (36.7%)	12 (20.0%)	17 (28.3%)
Income				
<10K	71 (46.1%)	21 (43.8%)	22 (42.3%)	28 (51.9%)
10K – 20K	43 (26.0%)	16 (33.3%)	12 (23.1%)	15 (27.8%)
>20K	40 (26.0%)	11 (22.9%)	18 (34.6%)	11 (20.4%)
Religion				
Christianity/Catholicism	65 (36.7%)	19 (31.7%)	27 (44.3%)	19 (33.9%)
Buddhism/Taoism	18 (10.2%)	6 (10.0%)	4 (6.6%)	8 (14.3%)
Non-religion	94 (53.1%)	35 (58.3%)	30 (49.2%)	29 (51.8%)
No. of Family Members (Mean ± SD)	3.04 ± 1.18	3.00 ± 1.21	3.22 ± 1.31	2.88 ± 0.96

p value is based on ANOVA for continuous data and chi-square for categorical data.

Table 2 Estimated Parameters of Linear Mixed Model for Beck Anxiety Inventory and Penn State Worry Questionnaire

	β	SE	95% CI
Beck Anxiety Inventory:			
Group x Time			
*MBCT * Immediate post*	**-5.05**	1.86	-8.72 – -1.38
*MBCT * 3 months post*	**-6.60**	1.89	-10.33 – -2.87
*PEG * Immediate post*	**-4.86**	1.86	-8.53 – -1.19
*PEG * 3 months post*	**-7.95**	1.81	-11.52 – -4.37
Penn State Worry Questionnaire:			
Group x Time			
*MBCT * Immediate post*	-1.99	1.95	-5.85 – 1.86
*MBCT * 3 months post*	-3.19	1.97	-7.07 – 0.70
*PEG * Immediate post*	-3.90	1.95	-7.75 – -0.05
*PEG * 3 months post*	**-4.24**	1.89	-7.98 – -0.51

** Significant effect in bold*

Figure 1 Mindfulness-Based Cognitive Therapy for Generalized Anxiety Disorder participant flow chart

Figure 2 Estimated mean scores in anxiety symptoms and worry symptoms of participants in Mindfulness-Based Cognitive Therapy (MBCT), Psycho-education (PEG) and the Usual Care (UC) group over the study period. Error bars represent the 95% Confident Intervals.

Figure 2a anxiety symptoms as measured by BAI

Figure 2b worry symptoms as measured by PSWQ

Figure 3 Estimated mean scores in other outcome measures of participants in Mindfulness-Based Cognitive Therapy (MBCT), Psycho-education (PEG) and the Usual Care (UC) group over the study period. Error bars represent the 95% Confident Intervals.

Figure 3a depressive symptoms as measured by CES-D

Figure 3b physical component of quality of life as measured by PCS12

Figure 3c mental component of quality of life as measured by MCS12

Figure 3d mindfulness as measured by FFMQ

Appendix

Appendix 1 Summary of MBCT session

Session 1: Automatic Pilot – identifying and stepping out of automatic pilot

- Group orientation
- Ground rules and introduction.
- Mindful eating: Raisin exercise and review
- Body scan practice and review

Session 2: Dealing with barriers – reactions to everyday events

- Body scan practice
- Practice and homework review
- Thoughts and feelings(anxiety) exercise
- Pleasant events calendar
- Sitting meditation

Session 3: Mindfulness of the breath – maintaining awareness using the breath as an anchor

- Sitting meditation
- Practice and homework review
- 3-minute breathing space and review
- Mindful stretching and review
- Mindful walking and review
- Unpleasant events calendar

Session 4: Staying present – to take a wider perspective and relate differently to experience

- Sitting meditation
- Practice and homework review

- Defining the 'territory' of Generalized Anxiety Disorder
- Explore common coping strategies (avoidance, safety behaviours, rumination/worry) versus taking a breathing space as the 'first step' before taking a wider view of what is happening.
- 3- minute breathing space (extended instructions) and review

Session 5: Allowing/letting be – acceptance of one's experience

- Sitting meditation (working with difficulties)
- Practice and homework review
- 3- minute breathing space and review

Session 6: Thoughts are not facts – seeing thoughts as mental events

- Sitting meditation (working with difficulties)
- Practice and homework review
- Mood (anxiety), thoughts and alternative viewpoints exercise
- 3- minute breathing space and review
- Discuss breathing space as the 'first step' before taking a wider view of thoughts

Session 7: How can I best take care of myself – developing an action plan

- Sitting meditation (includes working with difficulties)
- Practice and homework review
- Explore links between activity and mood
- Generate list of pleasure and mastery activities
- Plan how best to schedule such activities
- 3-minute breathing space as the 'first step' before choosing whether to take mindful action
- Identifying warning signs and actions to deal with them

- Identify realistic and meaningful goals for a life with satisfaction
- 3-minute breathing space or mindful walking

Session 8: Using what has been learnt to deal with future moods – linking practice to everyday life

- Body scan practice
- Practice and homework review
- Course review
- Discuss plans to maintain the practice and link them to positive reasons for doing so.
- End the classes with a concluding meditation (marble or stone)

Appendix 2: PEG Session Summary

Session 1: Preparing for stress control

- Introduction
- Course overview and how it works
- Describing your stress
- Introducing Stress diary
- Set goals for yourself

Session 2: Learning about stress

- Myths and facts about stress
- Thoughts, action and body: the TAB model
- The role of stress
- Different types of anxiety disorder
- The cause of stress
- What keeps stress going

Session 3: Controlling your body

- The role of body in stress
- The TAB model
- The body symptoms
- Progressive muscular relaxation

Session 4: Controlling your thoughts

- The role of thoughts in stress
- The TAB model
- The interaction of thoughts and stress
- Challenging your thoughts

    - The court case
    - Short cuts
    - Breaking up stress

Session 5: Controlling your action

- The role of action in stress
- The TAB model
- Avoidance and stress
- Four techniques when dealing with stress
    - Finding hidden problems
    - Exposure
    - Coping strategies
    - Problem solving

Session 6: Controlling your panic and insomnia

- **Panic**
    - The TAB vicious model
    - Controlling your panic body
    - Controlling your panic thoughts
    - Controlling your panic actions
- **Insomnia**
    - The TAB vicious model
    - Evaluating your insomnia
    - Treating your insomnia
    - Six steps to successful problem solving

Session 7: Controlling your depression

- The nature of depression

- Knowing the symptoms
- Learning to deal with your depression

Session 8: Trying it all together and controlling your future

- Review the course
- Stress control after the course ends

Appendix 3: The number of sessions participants attended in MBCT and PEG group.

No. of sessions attended	MBCT	PEG
0	2 (3.3%)	1 (1.6%)
3	3 (4.9%)	2 (3.3%)
4	4 (6.6%)	0
5	9 (14.8%)	4 (6.6%)
6	5 (8.2%)	6 (9.8%)
7	14 (23.0%)	14 (23.0%)
8	24 (39.3%)	34 (55.7%)