Mindfulness-based therapy for drug-resistant epilepsy

An assessor-blinded randomized trial

Venus Tang, PhD
Wai S. Poon, MBChB, FRCS
Patrick Kwan, MD, PhD

Correspondence to Dr. Tang: venustang@gmail.com

ABSTRACT

Objective: To investigate the effectiveness of mindfulness-based therapy (MT) and social support (SS) in patients with drug-resistant epilepsy.

Methods: We performed an assessor-blinded randomized control trial. Sixty patients with drug-resistant epilepsy were randomly allocated to MT or SS (30 per group). Each group received 4 biweekly intervention sessions. The primary outcome was the change in the total score of the Patient-Weighted Quality of Life in Epilepsy Inventory (QOLIE-31-P). Secondary outcomes included seizure frequency, mood symptoms, and neurocognitive functions. The assessors were blinded to the patient's intervention grouping. Results were analyzed using general linear model with repeated measure.

Results: Following intervention, both the MT (n = 30) and SS (n = 30) groups had an improved total QOLIE-31-P, with an improvement of +6.23 for MT (95% confidence interval [CI] +4.22 to +10.40) and +3.30 for SS (95% CI +1.03 to +5.58). Significantly more patients in the MT group had a clinically important improvement in QOLIE-31-P (+11.8 or above) compared to those who received SS (11 patients vs 4 patients). Significantly greater reduction in depressive and anxiety symptoms, seizure frequency, and improvement in delayed memory was observed in the MT group compared with the SS group.

Conclusions: We found benefits of short-term psychotherapy on patients with drug-resistant epilepsy. Mindfulness therapy was associated with greater benefits than SS alone in quality of life, mood, seizure frequency, and verbal memory.

Classification of evidence: This study provides Class II evidence that mindfulness-based therapy significantly improves quality of life in patients with drug-resistant epilepsy. ***Neurology*®** **2015;85:1100–1107**

GLOSSARY

AED = antiepileptic drug; **BAI** = Beck Anxiety Inventory; **BDI-II** = Beck Depression Inventory–II; **CI** = confidence interval; **hp2** = partial η^2; **MT** = mindfulness therapy plus social support; **PWE** = people with epilepsy; **QOL** = quality of life; **QOLIE-31-P** = Patient-Weighted Quality of Life in Epilepsy Inventory; **RCT** = randomized controlled trial; **SS** = social support.

The view that epilepsy and psychological disturbances share a bidirectional relationship has been supported by both population-based and experimental studies.[1–4] These findings have drawn recent attention to the potential role of psychobehavioral therapy for people with epilepsy (PWE). Trials examining different types of psychotherapy for PWE supported the use of cognitive-behavioral therapy–based approach and mind–body approach on improving psychological states and quality of life (QOL). Their effects on seizure control, however, are inconsistent.[5]

Mindfulness is a form of mental meditation that has become a popular health practice. The central element of mindfulness is to cultivate mindful attentional control by focusing on present-moment stimuli with nonjudgmental and acceptance attitude.[6,7] It has been incorporated into psychotherapy in recent decades.[8,9] Current evidence suggests that mindfulness could

Editorial, page 1094

Supplemental data at Neurology.org

From the Department of Clinical Psychology (V.T.), the Division of Neurosurgery, Department of Surgery, Faculty of Medicine (V.T., W.S.P.), and the Division of Neurology, Department of Medicine and Therapeutics, Faculty of Medicine (P.K.), Prince of Wales Hospital, The Chinese University of Hong Kong; and the Departments of Medicine and Neurology (P.K.), The University of Melbourne, Royal Melbourne Hospital, Australia.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

have benefits on a wide range of health measures, including mental well-being[10,11] (e.g., depressive and anxiety symptoms), physical conditions[12] (e.g., chronic pain), neurophysiologic markers[13–15] (e.g., immune system, cortical thickness, gray matter concentration), and cognitive functions[16,17] (e.g., learning, working memory). The effects of mindfulness on well-being and seizure control in PWE have been tested in a few randomized controlled trials (RCTs).[18,19] Despite methodologic limitations, their results suggested sustained benefits in QOL and seizure control in patients with drug-resistant epilepsy.

We undertook an assessor-blinded RCT to examine the effects of mindfulness therapy plus social support (MT) compared with social support alone (SS) as an attention placebo control among patients with drug-resistant epilepsy.

METHODS

Study objectives. The primary objective was to evaluate the effect of a 4 biweekly MT group on QOL in patients with drug-resistant epilepsy compared to a 4 biweekly SS group as attention placebo. The secondary objective was to evaluation the effect of each intervention on psychological states, seizure control, and neurocognitive functions.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee Review Board. Written informed consent was obtained from all participants. The trial was registered with clinicaltrials.gov (NCT02060422).

Participants. Patients were eligible for inclusion if they were 18 years or older with a diagnosis of epilepsy resistant to antiepileptic drug (AED) treatment according to the consensus definition by the International League Against Epilepsy.[20] Exclusion criteria included a primary diagnosis of organic mental disorder, psychotic disorders, psychogenic nonepileptic seizures, learning disability, or mental retardation. Patients were recruited from the neurology clinics of the Prince of Wales Hospital, a teaching hospital of the Chinese University of Hong Kong.

Procedures. Figure 1 shows the timeline of subject recruitment. Patients with drug-resistant epilepsy were referred by neurologists from the neurology clinics to a research assistant for recruitment. All referred patients were invited to participate and assessed for eligibility. Upon successful recruitment with signed informed consent, patients' demographic and clinical characteristics were collected. Randomization was performed by an independent research assistant. Patients were stratified by sex and age (by median split) into 4 blocks (young-female, young-male, old-female, old-male). Simple randomization by drawing was performed within each block to assign patients to one of the groups alternatively. Patients then received baseline assessment and entered a prospective baseline period of 6 weeks for seizure record on a diary, followed by an intervention period with 4 biweekly intervention sessions (either MT or SS) over 6 weeks. Postintervention assessment was conducted at 6 weeks after the last intervention session; seizures were recorded during this 6-week period. A team of trained research assistants with a bachelor's degree in psychology who were blinded to participants' intervention group performed all assessments; they were separated into 2 teams, one for baseline assessment and the other for postintervention assessment.

Intervention. Intervention comprised an active treatment condition: MT and an attention placebo control SS. Intervention was delivered in group format with four 2.5-hour biweekly sessions. Each group consisted of 7–8 participants; all interventions were conducted by the same clinical psychologist (V.T.).

Components of the interventions are listed in appendix e-1 on the *Neurology*® Web site at Neurology.org. All participants received an identical educational package on basic knowledge and management of epilepsy, including layman terms of the etiology and types of seizure, sleep hygiene, and importance of drug adherence and regular exercise. The MT protocol was designed based on several guiding references on mindfulness.[6,9,21,22] We emphasized the concept of mind–body connection that has been rooted in the Chinese culture. Furthermore, we incorporated mindfulness techniques with the concept of acceptance as coping with seizure-related disturbances, i.e., auras and postictal physical and psychological reactions.[21] Participants had experiential, progressive training on mindfulness techniques during sessions (appendix e-1). They were encouraged to have a 45-mintue daily mindfulness practice. No direct intervention was involved in the SS group. It was designed to provide a supportive atmosphere on their illness experiences and self-help strategies with the same contact hours and group format as the MT group.

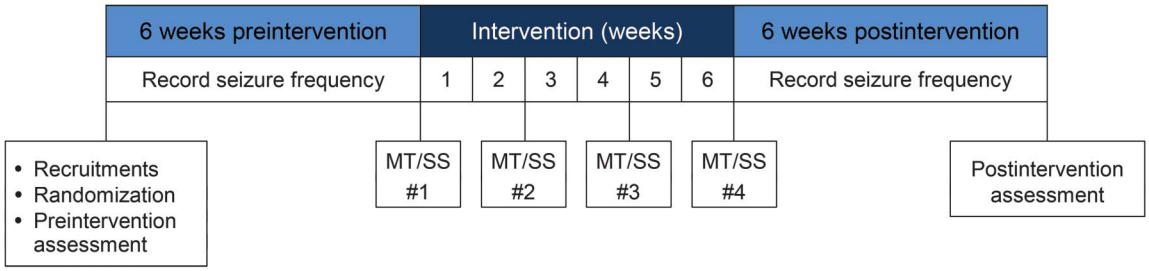
Outcomes. The primary outcome was the difference in the changes between the 2 groups in the total absolute score on the Patient-Weighted Quality of Life in Epilepsy Inventory (QOLIE-31-P). The total score reflects the patient's subjective well-being toward his or her QOL in various aspects related to epilepsy. Scores range between 0 and 100, with higher scores indicating better well-being. The criterion for a clinically important change was determined by >11.80 points of change in QOLIE-31-P total score.[23]

Secondary outcomes included measures of psychological states by Beck Depression Inventory–II (BDI-II) and Beck Anxiety Inventory (BAI); cognitive functions by the Chinese Auditory Verbal Learning Test, Rey Complex Figure Test and Recognition Trial, Category Fluency Test, Digit Span Test, and Stroop Color and Word Test–Victoria version; and seizure control in terms of number of seizures based on seizure diary and Seizure Severity Questionnaire. The references of all outcome measures are listed in appendix e-2.

Sample size. Using the QOLIE-31-P overall score as the primary outcome measure to detect a change in QOL, it was calculated that 60 patients with drug-resistant epilepsy (30 in each group) were needed to achieve statistical power of 0.8 to detect medium to large effect size of 0.74 of the QOLIE-31-P overall score at significant level of 0.05 in a 2-tailed test analysis.

Statistical analysis. We estimated the effect of intervention (i.e., MT vs SS) on change in the dependent variables using general linear model with repeated measures. Continuous data were tested for normality and logarithmic transformation was performed. Within-subject time factor (preintervention and postintervention change for both groups) and between-subject group factor (change from baseline for each group) were examined. Group-by-time interaction effect was used to estimate the differences of change between 2 groups. Null hypothesis was rejected with p value less than 0.05. Partial η^2 (hp2) was used to determine the effect size, with values of

Figure 1 Patient recruitment timeline



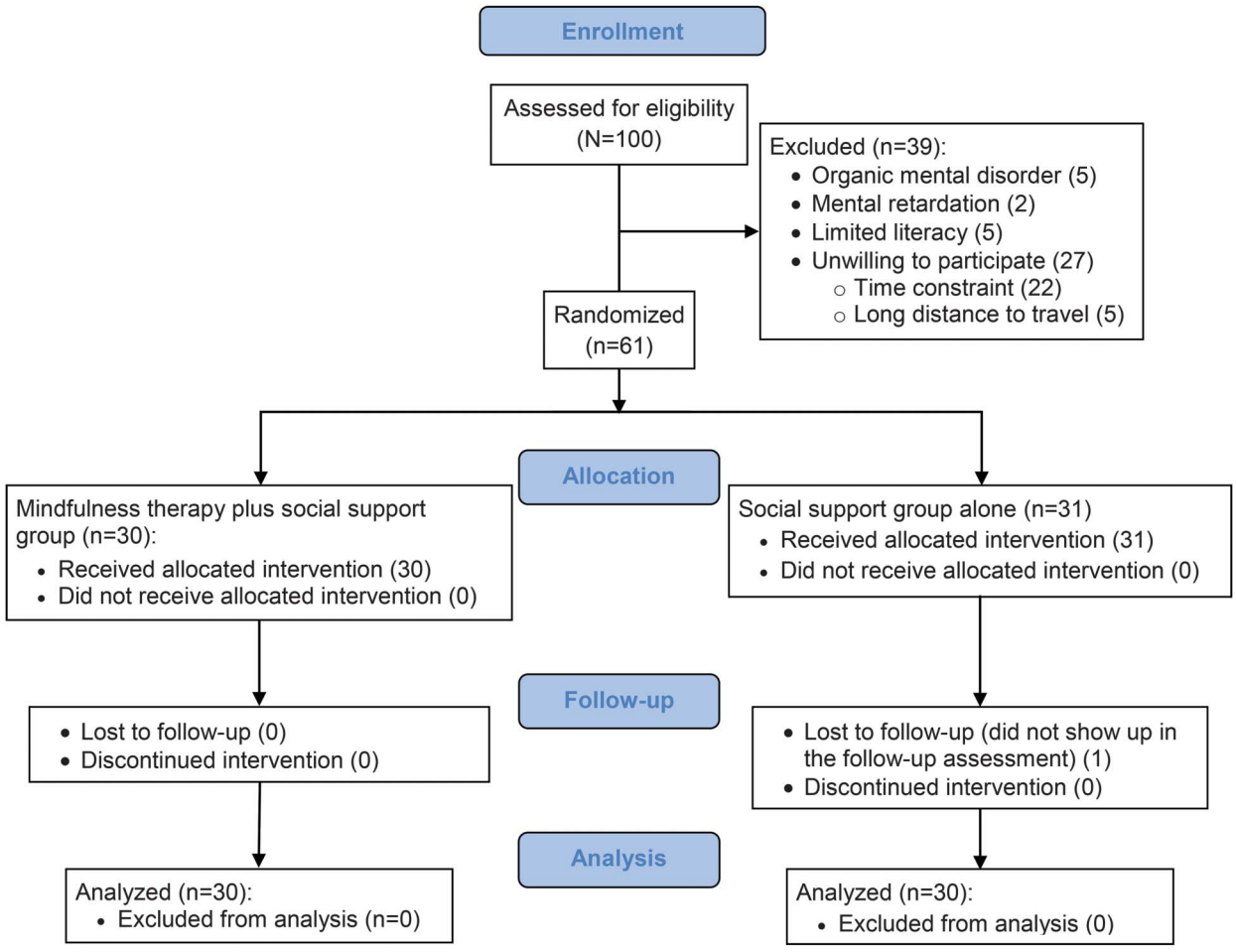
MT = mindfulness therapy plus social support; SS = social support.

0.01–0.06, 0.06–0.14, and >0.14 representing small, medium, and large effect sizes, respectively.[24,25] The χ^2 test was performed to compare the number of patients who had clinically important change in QOLIE-31-P from baseline to postintervention assessment between the 2 groups. Phi coefficient (φ) was used to determine the effect size, with values of <0.20, 0.20–0.60, and >0.60 representing small, medium, and large effect size, respectively.[25,26] McNemar test was used to analyze the difference in patients who had change in the severity category of BAI and BDI-II at baseline and postintervention in the 2 groups. Statistical analysis was performed using IBM (Armonk, NY) SPSS version 20.0.

Classification of level of evidence. This study provides Class II evidence that mindfulness-based therapy significantly improves QOL in patients with drug-resistant epilepsy.

RESULTS The study was carried out between September 2011 and January 2013. There was no change to the methods after trial commencement. We invited a total of 100 patients with drug-resistant epilepsy to participate. The most commonly cited reasons for unwillingness to participate (n = 27) were time constraints (n = 22) and long distant to

Figure 2 Flowchart of the study participants



travel (n = 5). Of the 61 who were willing to participate in the study, all met the inclusion criteria and were successfully enrolled and randomized. One patient did not show up to the postintervention evaluation, thus a total of 60 completed data (30 in each group) were analyzed (figure 2). Patients in the 2 groups had similar demographics and clinical characteristics (table 1). All patients indicated that they had not participated in any group psychological intervention. No patient reported experience of meditation practice. There was no adverse event during or after the interventions. Tables 2 and 3 show the preintervention and postintervention scores and changes in all dependent variables with 95% confidence interval (CI).

Quality of life. The mean of the QOLIE-31-P total at postintervention statistically improved in both groups with a large effect size ($F_{1,58} = 30.35$, $p < 0.001$, hp2 = 0.334, 95% CI +3.38, +7.24). Group-by-time interaction was not significant. However, more patients in the MT group had clinically important improvement on QOLIE-31-P total score (11/30; 36.6%) compared to the SS group (4/30; 13.3%). The difference was significant with a medium effect size [χ^2 (1) = 4.356, $p = 0.037$, $\varphi = 0.269$]. The number needed to treat for the MT group was 4.29 (95% CI 2.25, 44.83) with an absolute risk reduction of 23.3% (95% CI 2%, 44%).

Statistically significant improvements were found in other aspects of QOL by within-subject tests, including energy ($F = 12.51$, $p = 0.001$, hp2 = 0.177, 95% CI +2.14, +8.02), mood ($F = 7.04$, $p = 0.010$, hp2 = 0.108, 95% CI +1.16, +8.27), medication effect ($F = 4.38$, $p = 0.041$, hp2 = 0.070, 95% CI +0.23, +8.80), and seizure worry ($F = 34.02$, $p < 0.001$, hp2 = 0.370, 95% CI +2.90, +11.19). There was no significant group-by-time interaction.

Table 1 Clinical and demographic characteristics

	Mindfulness group (n = 30)	Social support group (n = 30)
Age, y, mean (SD)	34.77 (10.26)	35.47 (11.22)
M:F, n (%)	14 (46.7):16 (53.3)	14 (46.7):16 (53.3)
% Right-handed	96.7	86.7
Age at onset, y, mean (SD)	14.33 (9.56)	16.87 (12.48)
Disease duration, y, mean (SD)	20.43 (9.95)	18.93 (11.08)
Total seizures in 6 wk preintervention, mean (SD)	9.83 (9.78)	9 (11.79)
Last seizure, % within 1 wk	40	36.7
Epileptic foci, % temporal	43.3	33.3
No. of current epileptic drugs, %		
Monotherapy	36.7	40.0
Two	23.3	40.0
Three	36.7	16.7
Four or more	3.3	3.3
Most commonly used AEDs, %		
Carbamazepine	50	40
Valproate	30	36.7
Lamotrigine	26.7	26.7
Levetiracetam	30	26.7
Epileptic foci, % temporal	43.3	33.3
Concomitant nonpsychiatric illness, n	5	5
Concomitant psychiatric illness, n	3	2
Educational level, % ≥11 y	76.7	80
Occupation, % full-time employment	56.7	53.3

Mood. Patients in both groups had a statistically significant reduction in BAI scores after intervention; within-subject test revealed significant main effect of time ($F = 23.44$, $p < 0.001$, hp2 = 0.288, 95% CI −6.44, −1.76). Group-by-time interaction effect was significant with a medium to large effect size ($F = 7.46$, $p = 0.008$, hp2 = 0.114). In the MT group, 12 (40%) reported moderate to severe anxiety at baseline (raw score ≥16). After intervention, 10 (33.3%) became mild or asymptomatic (raw score ≤15), 2 (6.7%) were unchanged, and 1 (3.3%) changed for the worse and became moderately to severely anxious from a mild level at baseline. In the SS group, 10 (33.3%) had moderate to severe anxiety at baseline. After intervention, 9 (30.0%) became mild or asymptomatic, 1 (3.3%) was unchanged, and 2 (6.7%) deteriorated and became moderately to severely anxious. According to McNemar tests, a clinically significant difference in terms of the number of patients who had change of severity category preintervention and postintervention was demonstrated only in the MT group ($p = 0.012$) but not the SS group ($p = 0.065$). While there was a statistically significant reduction in the scores of BAI in both groups, clinical significance was demonstrated only in the MT group.

For BDI-II, within-subject test revealed significant main effect of time ($F = 43.66$, $p < 0.001$, hp2 = 0.429, 95% CI −6.39, −3.21), suggesting a statistically significant reduction of BDI-II scores in both groups after treatment. Group-by-time interaction was significant with a medium effect size ($F = 4.19$, $p = 0.045$, hp2 = 0.067). Seven patients (23.3%) in each group had a moderate to severe range (raw scores ≥20) of depression at baseline. After intervention, 4 (13.3%) improved to mild or asymptomatic (raw scores ≤19) and 3 (10.0%) were unchanged in each group. No patient changed for the worse. There was no statistically significant difference on change of severity category preintervention and postintervention ($p = 0.125$ for both groups). This suggested that

Table 2 Preintervention and postintervention scores and changes in primary outcomes

	Mindfulness group (n = 30)			Social support group (n = 30)		
QOLIE-31-P	Baseline	Postintervention	Changes	Baseline	Postintervention	Changes
Total	57.14 (52.68, 61.65)	63.39 (59.16, 67.62)	+6.23 (+4.22, +10.40)	59.34 (53.79, 64.89)	62.64 (57.69, 67.59)	+3.30 (+1.03, +5.58)
Energy	26.92 (21.23, 32.60)	34.75 (27.18, 42.32)	+7.83 (+3.47, +12.19)	35.29 (25.94, 44.64)	37.63 (29.36, 45.89)	+2.33 (−1.61, +6.28)
Mood	34.67 (28.56, 40.78)	41.17 (33.66, 48.67)	+6.50 (+0.64, +12.36)	43.63 (34.98, 52.29)	46.57 (37.77, 55.37)	+2.93 (−1.37, +7.24)
Daily activities	38.82 (28.73, 48.90)	40.21 (30.20, 50.22)	+1.39 (−6.27, +9.05)	49.81 (37.97, 61.64)	54.09 (42.77, 65.41)	+4.29 (−3.15, +11.73)
Cognitive effect	35.43 (28.31, 42.55)	41.86 (32.76, 50.95)	+6.43 (−1.90, +14.76)	37.98 (28.24, 47.73)	40.25 (31.01, 49.49)	+2.27 (−1.60, +6.14)
Medication effect	33.82 (26.48, 41.15)	37.90 (31.28, 44.54)	+4.08 (−3.41, +11.57)	35.44 (26.56, 44.32)	40.39 (31.67, 49.12)	+4.95 (+0.27, +9.64)
Seizure worry	23.37 (16.77, 29.96)	32.46 (22.90, 42.03)	+9.09 (+1.31, +16.87)	32.89 (23.02, 42.76)	37.88 (28.33, 47.43)	+4.99 (+1.62, +8.36)

Abbreviation: QOLIE-31-P = Patient-Weighted Quality of Life in Epilepsy Inventory.
Scores presented as mean (95% confidence interval).

although there was a statistically significant reduction in BDI-II scores in both groups, this difference was of no clinical significance.

Cognitive functions. Within-subject test revealed a significant improvement over time on 2 trials of verbal memory: recall after interference and delayed recall (F = 17.66, $p < 0.001$, hp2 = 0.233, 95% CI +0.49, +1.47; and F = 28.43, $p < 0.001$, hp2 = 0.329, 95% CI +0.69, +1.81 for the 2 trials, respectively). Group-by-time interaction effects were significant for both (F = 6.21, p = 0.016, hp2 = 0.097; and F = 25.48, $p < 0.001$, hp2 = 0.305) with medium to large effect sizes. Within-subject improvement was significant for 3 measures on verbal recognition memory. Results showed increased number of recognition correct hit (F = 4.37, p = 0.041, hp2 = 0.070, 95% CI +0.13, +0.58), reduction of recognition false alarm (F = 15.06, $p < 0.001$, hp2 = 0.206, 95% CI −1.15, −0.28), and increased percentage correct recognition (F = 17.97, $p < 0.001$, hp2 = 0.237, 95% CI +1.00, +3.07). Significant group-by-time interaction suggested that patients in the MT group had less false alarm in recognition (F = 10.95, p = 0.002, hp2 = 0.155) and increased on the percentage of correct recognition (F = 10.67, p = 0.002, hp2 = 0.155) than patients in the SS group.

For nonverbal memory function, within-subject increases were significant on both immediate recall (F = 15.63, $p < 0.001$, hp2 = 0.212, 95% CI +1.85, +4.54) and delayed recall (F = 14.63, $p < 0.001$, hp2 = 0.201, 95% CI +1.13, +3.69). There was no significant group-by-time interaction. No change was observed in nonverbal recognition.

There were neither within-subject nor between-subject differences on Category Fluency Test, Digit Span Test, or Stroop Color and Word Test–Victoria version.

Seizure control. Seizure frequency was significantly reduced in the within-subject test (F = 25.51, $p < 0.001$, hp2 = 0.306, 95% CI −3.96, −1.64). Group-by-time interaction was statistically significant (F = 5.90, p = 0.018, hp2 = 0.092) with a medium to large effect size. Although within-group test showed a statistically significant reduction in seizure severity (F = 15.28, $p < 0.001$, hp2 = 0.209, 95% CI −0.91, −0.29), there was no significant difference between the 2 groups.

DISCUSSION In this RCT, we found benefits of group-based short-term psychobehavioral therapies in patients with drug-resistant epilepsy on improving QOL and mood and reducing seizure frequency and severity. More patients had a clinically important improvement in QOL in the mindfulness therapy group compared to social support alone. Mindfulness therapy was also found to improve anxiety with

Table 3 Preintervention and postintervention scores and changes in secondary outcomes

	Mindfulness group (n = 30)			Social support group (n = 30)		
	Baseline	Postintervention	Changes	Baseline	Postintervention	Changes
Psychological measures						
BDI-II	12.43 (9.33, 15.54)	6.90 (4.49, 9.31)	−5.53 (−7.28, −3.79)	13.53 (9.84, 17.23)	9.47 (6.26, 12.67)	−4.07 (−6.62, −1.31)[a]
BAI	15.10 (11.38, 18.82)	9.73 (6.25, 13.22)	−5.37 (−8.52, −2.21)	13.53 (9.09, 17.97)	10.70 (7.24, 14.16)	−2.83 (−6.43, +0.76)[a]
Seizure indexes						
Seizure frequency in 6 wk	9.83 (6.18, 13.48)	5.90 (2.88, 8.92)	−3.93 (−5.79, +2.08)	9.00 (4.59, 13.40)	7.33 (3.46, 11.21)	−1.67 (−3.03, −0.30)[a]
Seizure Severity Index	3.31 (2.69, 3.92)	2.55 (2.06, 3.03)	−0.76 (−1.21, −0.32)	3.35 (2.76, 3.95)	2.91 (2.44, 3.38)	−0.44 (−0.89, +0.00)
Neurocognitive tests						
Verbal memory (CAVLT)						
ImmR	44.53 (41.40, 47.67)	54.37 (51.05, 57.68)	+9.83 (+6.28, +13.39)	44.97 (41.54, 48.39)	47.50 (43.82, 51.17)	+2.53 (+0.88, +4.18)
ImmRA	9.90 (9.00, 10.79)	11.47 (10.48, 12.46)	+1.57 (+0.66, +2.47)	10.03 (9.16, 10.90)	10.43 (9.63, 11.23)	+0.40 (+0.08, +0.72)[a]
DelR	9.03 (8.08, 9.99)	11.47 (10.43, 12.51)	+2.43 (+1.59, +3.28)	10.00 (9.09, 10.90)	10.07 (9.09, 11.05)	+0.70 (−0.38, +0.52)[a]
DelReco	13.50 (13.06, 13.94)	14.03 (13.69, 14.38)	+0.53 (+0.11, +0.96)	13.53 (12.96, 14.11)	13.60 (13.10, 14.09)	+0.70 (−0.32, +0.46)
DelFA	2.70 (1.82, 3.58)	1.43 (0.59, 2.28)	−1.27 (−2.05, −0.48)	3.03 (1.79, 4.27)	2.86 (1.67, 4.06)	−0.17 (−0.49, +0.16)[a]
RPC	91.6 (89.68, 93.52)	95.20 (93.26, 97.14)	+3.60 (+1.87, +5.33)	91.00 (87.83, 94.17)	91.47 (88.66, 94.27)	+0.47 (−0.47, +1.40)[a]
Nonverbal memory (RCFT)						
ImmR	19.25 (16.45, 22.05)	24.03 (21.02, 27.05)	+4.78 (+2.40, +7.17)	19.12 (16.53, 21.71)	20.72 (18.29, 23.14)	+1.60 (+0.49, +2.71)
DelR	19.95 (17.23, 22.67)	23.48 (20.69, 26.28)	+3.53 (+1.19, +5.87)	19.92 (17.36, 22.47)	21.20 (18.71, 23.69)	+1.28 (+0.21, +2.36)
DelReco	20.17 (19.46, 20.87)	20.70 (19.95, 21.48)	+0.53 (−0.10, +1.17)	19.77 (19.96, 20.57)	19.43 (18.47, 20.39)	−0.33 (−0.81, +0.15)
Category Fluency Test	26.50 (23.23, 29.77)	29.27 (26.09, 32.44)	+2.76 (−0.03, +5.57)	27.63 (25.40, 29.86)	28.27 (26.22, 30.31)	+0.63 (−0.48, +1.75)
DS forward sequence	8.43 (7.89, 8.97)	8.60 (8.09, 9.11)	+0.17 (−0.32, +0.66)	8.40 (8.05, 8.75)	8.27 (7.89, 8.65)	−0.13 (−0.41, +0.14)
DS backward sequence	5.17 (4.59, 5.75)	5.80 (5.22, 6.38)	+0.63 (+0.83, +1.18)	5.30 (4.70, 5.89)	5.50 (4.93, 6.07)	+0.20 (−0.07, +0.47)
Stroop test						
DotRT, s	15.43 (13.29, 17.57)	14.23 (12.26, 16.21)	−1.19 (−2.60, +0.22)	14.21 (12.04, 16.38)	14.59 (13.15, 16.04)	+0.38 (−0.92, +1.68)
WordRT, s	19.71 (15.70, 23.27)	16.30 (13.56, 19.05)	−3.41 (−6.58, +0.24)	17.52 (15.10, 19.94)	18.26 (15.48, 21.03)	+0.73 (−1.11, +1.58)
CWRT, s	26.67 (22.40, 30.93)	25.49 (19.46, 31.52)	−1.18 (−6.42, +4.06)	25.13 (22.29, 27.96)	24.45 (21.68, 27.24)	−0.67 (−1.25, −0.89)
IF, s	11.23 (8.31, 14.15)	11.25 (6.74, 15.76)	+0.02 (−4.76, +4.80)	10.92 (8.78, 13.05)	9.86 (7.71, 12.01)	−1.05 (−2.66, +0.56)

Abbreviations: BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; CAVLT = Chinese Auditory Verbal Learning Test; CWRT = Color-Word Trial reaction time; DelFA = delayed recognition false alarm; DelR = delayed recall; DelReco = delayed recognition; DotRT = Dot Trial reaction time; DS = Digit Span Test; IF = interference; ImmR = immediate recall; ImmRA = immediate recall after interference; RCFT = Rey Complex Figure Test; RPC = recognition percentage correct; RT = reaction time; WordRT = Word Trial reaction time.
Scores presented as mean (95% confidence interval).
[a] Statistically significant group-by-time interaction at $p < 0.05$.

clinical significance. Although our results demonstrated statistical improvement on several cognitive measures including verbal and nonverbal memory, the findings should be interpreted with caution as practice effects cannot be ruled out.

There has been increasing research interest in the role of psychobehavioral therapy in epilepsy. The occurrence of an epileptic seizure has been hypothesized as an endpoint of multiple precipitating factors, including general stress, risk factor (e.g., missed medication), trigger (e.g., visual stimuli, cognitive or emotional triggers), and warning (i.e., prodromal phase and aura).[5] Under this model, psychobehavioral therapy may increase an individual's ability to resist the buildup of these precipitants, probably through improving epilepsy knowledge and adjustment, managing stress, and reducing psychiatric comorbidities.[5] Based on this hypothesis, we found that mindfulness therapy had positive effects on PWE beyond subjective QOL but also extended to mood, seizure frequency, and cognitive performance. Our results were consistent with previous reports that found significant effects of mindfulness-based therapy on seizure frequency and QOL compared to supportive therapy alone.[19]

Despite positive evidence, the mechanism of mindfulness has not been clearly understood. Mindfulness practice facilitates a sense of nonjudgmental acceptance towards internal bodily sensations, mental processes, and external stimuli. This process has been hypothesized to cultivate a habit of pure awareness and attention at present, hence reducing emotional interpretation and judgments that often underlie emotional distress.[7,8,10,27,28] In mood disorders, it was believed that being aware of negative emotions and allowing the presence of those feelings with an acceptance attitude could lessen distress.[7,29,30] In PWE, there was a notion that instead of struggling to avoid seizures, an acceptance of its occurrence might paradoxically have an inhibiting effect.[26,28] In our mindfulness-based therapy, patients were trained to recognize and accept rather than avoid the feelings associated with seizure, e.g., fear of seizure and bodily discomfort. This mindful acceptance likely contributed to improved seizure control.

Our study also found improvement in delayed verbal memory in the mindfulness therapy group that was significantly more substantial than in the social support group. Some studies demonstrated the effects of mindfulness on improved working memory, and attributed this to increased cognitive capacities that prevented newly learned materials from being lost despite exposure to stressful stimuli.[24] In our test settings, patients were exposed to interferences between the initial learning phase and the delayed verbal memory test. Mindfulness practice possibly enhanced their abilities to retain and retrieve newly learned information and differentiate target words from noises after interferences.

The general improvement in QOL in patients who received social support could be explained by a few reasons. First, all patients received an educational package including epilepsy knowledge and lifestyle recommendations. Studies have consistently showed that improved knowledge alone could have a positive impact on psychosocial outcomes in PWE.[31,32] Furthermore, group participation itself might contribute to such improvement, since socialization is an important determinant of QOL.[33] It has been shown that PWE who attended a social support group had a more positive attitude on future outlook compared to those who did not.[34] Peer gatherings provide a supportive platform for the exchange of similar experiences; such a process possibly contributed to a better sense of well-being.

Some limitations of this study should be noted. Generalizability of the findings was limited by the hospital-based, single-center design. The benefits of seizure control, mood, and neurocognitive functions were secondary outcomes and should be viewed as exploratory. Since parallel versions of the cognitive tests were not available, practice effect was not controlled. The long-term therapeutic effects were not measured. In addition, an untreated control group was lacking, although including one was considered ethically difficult. The amount of time spent on mindfulness practice outside therapeutic sessions was not measured. Due to ethical reasons, medication change was not prohibited. Nonetheless, AED regimen was adjusted between the preintervention and postintervention assessments in only one patient in the SS group. Furthermore, effects of AEDs on cognitive and psychological functions might have confounded our results in mood and neurocognitive functions, although the types of AEDs taken by both groups were similar (table 1).

This study provides evidence that mindfulness therapy delivered with social support is more effective than social support alone in improving QOL and reducing anxiety of patients with drug-resistant epilepsy. Both mindfulness therapy and social support appear to benefit the well-being, seizure control, and cognitive function in this patient group. Future research may include a waitlist control design, with long-term evaluation of the sustainability of therapeutic effects coupled with more objective measures of changes such as neuroimaging.

AUTHOR CONTRIBUTIONS

Dr. Tang designed the study, obtained the data, performed statistical analysis, interpreted the data, and drafted and approved the final version of the manuscript. Dr. Poon designed the study, supervised the execution, and approved the final version of the manuscript. Dr. Kwan designed the study, supervised the execution, coordinated the data analysis plan,

interpreted the data, contributed to revision for important intellectual content, and approved the final version of the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received October 21, 2014. Accepted in final form April 23, 2015.

REFERENCES

1. Hesdorffer DC, Hauser WA, Olafsson E, Ludvigsson P, Kjartansson O. Depression and suicide attempt as risk factors for incident unprovoked seizures. Ann Neurol 2006;59:35–41.
2. Chang YT, Chen PC, Tsai IJ, et al. Bidirectional relation between schizophrenia and epilepsy: a population-based retrospective cohort study. Epilepsia 2011;52:2036–2042.
3. Kanner AM, Byrne R, Chicharro A, Wuu J, Frey M. A lifetime psychiatric history predicts a worse seizure outcome following temporal lobectomy. Neurology 2009; 72:793–799.
4. Jones NC, O'Brien TJ. Stress, epilepsy, and psychiatric comorbidity: how can animal models inform the clinic? Epilepsy Behav 2013;26:363–369.
5. Tang V, Michaelis R, Kwan P. Psychobehavioral therapy for epilepsy. Epilepsy Behav 2014;32:147–155.
6. Kabat-Zinn J. Mindfulness-based interventions in context: past, present, and future. Clin Psychol Sci 2003;10:144–156.
7. Segal ZV, Teasdale JD, Williams J, Mark G. Mindfulness-based cognitive therapy: theoretical rationale and empirical status. In: Hayes SC, Follette VM, Linehan MM, editors. Mindfulness and Acceptance: Expanding the Cognitive-behavioral Tradition. New York: Guilford Press; 2004.
8. Chambers R, Gullone E, Allen NB. Mindful emotion regulation: an integrative review. Clin Psychol Rev 2009;29: 560–572.
9. Hofmann SG, Sawyer AT, Fang A. The empirical status of the "new wave" of cognitive behavioral therapy. Psychiatr Clin N Am 2010;33:701–710.
10. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: a meta-analytic review. J Consult Clin Psychol 2010;78: 169–183.
11. Piet J, Hougaard E. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. Clin Psychol Rev 2011;31:1032–1040.
12. Chiesa A, Serretti A. Mindfulness-based interventions for chronic pain: a systematic review of the evidence. J Altern Complement Med 2011;17:83–93.
13. Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in brain and immune function Produced by mindfulness meditation. Psychosom Med 2003;65:564–570.
14. Lazar SW, Kerr CE, Wasserman RH, et al. Meditation experience is associated with increased cortical thickness. Neuroreport 2005;16:1893–1897.
15. Hölzel BK, Carmody J, Vangel M, et al. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res 2011;191:36–43.
16. Mrazek MD, Franklin MS, Phillips DT, Baird B, Schooler JW. Mindfulness training improves working memory capacity and GRE performance while reducing mind wandering. Psychol Sci 2013;24:776–781.
17. Chiesa A, Calati R, Serretti A. Does mindfulness training improve cognitive abilities? A systematic review of neuropsychological findings. Clin Psychol Rev 2011;31:449–464.
18. Lundgren T, Dahl J, Yardi N, Melin L. Acceptance and commitment therapy and yoga for drug-refractory epilepsy: a randomized controlled trial. Epilepsy Behav 2008;13:102–108.
19. Lundgren T, Dahl J, Melin L, Kies B. Evaluation of acceptance and commitment therapy for drug refractory epilepsy: a randomized controlled trial in South Africa: a pilot study. Epilepsia 2006;47:2173–2179.
20. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–1077.
21. Dahl J, Lundgren T. Analysis and treatment of epilepsy using mindfulness, acceptance, values, and countermeasures. In: McCracken LM, editor. Mindfulness and Acceptance in Behavioral Medicine. Oakland, CA: New Harbinger Publications; 2011.
22. Kabat-Zinn J. Coming to Our Senses: Healing Ourselves and the World through Mindfulness. New York: Hyperion; 2006.
23. Wiebe S, Matijevic S, Eliasziw M, Derry PA. Clinically important change in quality of life in epilepsy. J Neurol Neurosurg Psychiatry 2002;73:116–120.
24. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol 2013;4:863.
25. Cohen J. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.
26. Rea LM, Parker RA. Designing and Conducting Survey Research. San Francisco, CA: Jossey-Bass; 1992.
27. Baer RA. Mindfulness-based Treatment Approaches: Clinician's Guide to Evidence Base and Applications. Waltham, MA: Elsevier Academic Press; 2006.
28. Anderson ND, Lau MA, Segal ZV, Bishop SR. Mindfulness-based stress reduction and attentional control. Clin Psychol Psychother 2007;14:449–463.
29. Hofmann SG, Asmundson GJ. Acceptance and mindfulness-based therapy: new wave or old hat? Clin Psychol Rev 2008; 28:1–16.
30. Hölze BK, Lazar SW, Gard T, Schuman-Olivier Z, Vago DR, Ott U. How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. Perspect Psychol Sci 2011;6:537–559.
31. May TW, Pfafflin M. The efficacy of an educational treatment program for patients with epilepsy (MOSES): results of a controlled, randomized study: Modular Service Package Epilepsy. Epilepsia 2002;43:539–549.
32. Frizzell CK, Connolly AM, Beavis E, Lawson JA, Bye AME. Personalised epilepsy education intervention for adolescents and impact on knowledge acquisition and psychosocial function. J Paediatr Child Health 2011;47: 271–275.
33. Gillham R, Bryant-Comstock L, Kane K. Validation of the side effect and life satisfaction (SEALS) inventory. Seizure 2000;9:458–463.
34. Chung K, Liu Y, Ivey SL, et al. Quality of life in epilepsy (QOLIE): insights about epilepsy and support groups from people with epilepsy (San Francisco Bay Area, USA). Epilepsy Behav 2012;24:256–263.