

REVIEW

Effectiveness of mindfulness-based intervention on psychotic symptoms for patients with schizophrenia: A meta-analysis of randomized controlled trials

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Abstract

Aims: To evaluate the effects of mindfulness-based intervention on psychotic symptoms, positive symptoms, negative symptoms, depressive symptoms, anxiety, and rehospitalization.

Design: A meta-analysis of randomized controlled trials.

Data Sources: Medline, Embase, Cochrane Central Register of Controlled Trials, PsycINFO, CINAHL, National Digital Library of Theses and Dissertations in Taiwan, and Airtiti Library were searched from their earliest available date up to April 2019.

Review Methods: The guidelines of the Cochrane Collaboration were followed to report this systematic review. Two authors conducted this meta-analysis independently.

Results: Nine randomized controlled trials were included. Meta-analysis showed that mindfulness-based intervention significantly decreased psychotic symptoms, positive symptoms, negative symptoms, depressive symptoms, and duration of rehospitalization among patients with schizophrenia, and that the reduction in negative symptoms lasted through short-term follow-up. The moderation analysis showed that significantly decreased positive symptoms occurred in the nurse-led intervention group, while no significant impact was found in the psychologist-led intervention group.

Conclusion: The psychotic symptoms of the patients with schizophrenia are improved after mindfulness-based intervention and the effects on the negative symptoms can be maintained for at least 3 to 6 months. Mindfulness-based intervention provided by nurses produces more improvements in positive symptoms than intervention provided by psychologists.

Impact: A growing number of mindfulness-based interventions have been implemented for patients with schizophrenia, although the effectiveness had not previously been established by meta-analysis. Mindfulness-based interventions appear to reduce the symptom severity of schizophrenia patients. Further suggestions for healthcare providers and researchers are provided and discussed.

KEYWORDS

meta-analysis, mindfulness, nurses, nursing, psychosis, schizophrenia

1 | INTRODUCTION

Estimates of prevalence of schizophrenia worldwide range from 0.25-0.75% of the population (National Institute of Mental Health, 2019). The prevalence rates have increased in the past 10 years in Asian societies (Chan et al., 2015; Ministry of Health & Welfare, 2019). Psychotic symptoms, the core symptoms manifested by schizophrenia, consist of positive and negative symptoms (American Psychiatric Association, 2013). Positive symptoms, including hallucination and delusions, influence the patients' social interactions and daily activities (Coid et al., 2013). Negative symptoms, such as emotional withdrawal, blunted affect, passive social withdrawal, and poor rapport, have greater impacts on patient functioning than positive symptoms (Rabinowitz et al., 2012). It is noted that a large percentage schizophrenic patients suffer from depressive symptoms, which were associated with side effects of medications and poor psychological responses to stress (Upthegrove et al., 2017; Xu et al., 2018).

Antipsychotics and antidepressants are the primary medical treatments for psychotic symptoms (Ballon & Stroup, 2013; Remington et al., 2016). However, medication failed to achieve remission from schizophrenia in up to 30%-70% of patients (Ballon & Stroup, 2013; Stroup & Marder, 2015). In addition to medication, cognitive behavioural therapy (CBT), a non-pharmacological treatment, has been used to treat psychosis for patients with schizophrenia (NICE, 2014). However, a review study found limited effects of conventional CBT on reducing psychotic symptoms (Jauhar et al., 2019). In recent years, mindfulness-based intervention, a novel branch of CBT, was developed for patients with schizophrenia (Cramer et al., 2016; Louise et al., 2018).

Through mindfulness meditation practice, patients learn to observe sensations and their reactions to them without judgment and through which they let go of self-defeating habitual reactions to difficult life experiences (Chadwick, 2014). From the perspective of the cognitive neuropsychiatric model of delusions (Blackwood et al., 2001), decreasing inferential biases through mindfulness can reduce the formation of delusions. Another study found that mindfulness of hearing voices was negatively correlated with voice-related distress and reduced responsiveness to voices (Stephanie et al., 2018). Systematic reviews and meta-analyses found that mindfulness-based intervention alone or combined with acceptance commitment therapy (ACT) reduced psychotic symptoms and rehospitalization among patients with mental illness (Aust & Bradshaw, 2017; Cramer et al., 2016; DiGiorgio et al., 2016; Louise et al., 2018; Potes et al., 2018). These studies, which included patients with a variety of types of mental illness, can be used to specifically demonstrate the effects of mindfulness-based intervention in the subset of patients with schizophrenia. Mindfulness-based intervention needs to be modified to manage psychotic symptoms of schizophrenic patients (Chadwick, 2006). However, there are few meta-analyses to specifically examine the effects of mindfulness-based intervention developed for patients with schizophrenia. Moreover, the effects of mindfulness-based intervention on

negative symptoms and depressive symptoms are not well-studied. Our meta-analysis study aimed to confirm the effects of mindfulness-based intervention as a complementary intervention in patients with schizophrenia.

1.1 | Background

Current pharmacotherapy for schizophrenia is insufficient for many patients. With pharmacotherapy, only 70% patients with schizophrenia experienced their positive symptoms eliminated or reduced to a tolerable level (Stroup & Marder, 2015). Pharmacological and physical therapy also have limited ability to decrease negative symptoms (Fusar-Poli et al., 2015). Other recent studies found that non-pharmacological interventions including psychological and psychosocial interventions could improve positive symptoms (Bighelli et al., 2018) and negative symptoms (Lutgens et al., 2017). The findings of a recent meta-analysis study demonstrate that psychotherapy contributes to the positive effects on improving positive symptoms for schizophrenic patients with medication treatment resistance (Polesse et al., 2019). However, it remains not clear about the impacts of psychotherapy on negative symptoms for this study subjects.

Previous studies found that conventional cognitive behavioural therapy (CBT) aiming to manage the cognitive distortions only led to small-to-moderate reductions in psychotic symptoms (Jauhar et al., 2019; Naeem et al., 2016). However, high dropout rates from conventional CBT suggest low clinical feasibility of this treatment modality (Bighelli et al., 2018). The third-wave CBT, mindfulness-based therapy (e.g., mindfulness-based cognitive therapy, MBCT), and ACT emphasize paying attention to present-moment experiences without making judgment and focusing on the contextual awareness not to emotionally attach to the contents (Hayes & Hofmann, 2017; Kabat-Zinn, 1994). This is different from conventional CBT, which focuses on cognitive contents while debating the rationale of the thoughts (Jackson et al., 2009). Notably, the dropout rate for mindfulness intervention was lower than for other types of psychological interventions (Bighelli et al., 2018).

Meta-analyses found that overall, mindfulness-based intervention alone or combined with ACT was effective at reducing psychotic symptoms (Cramer et al., 2016; Louise et al., 2018) and rehospitalization (Cramer et al., 2016), but not effective at improving positive symptoms (Cramer et al., 2016). There are some limitations of these studies. The systematic reviews included some studies that did not use a randomized controlled design to demonstrate the effects of mindfulness-based intervention. The meta-analyses, including all studies with randomized controlled trials (RCT), included study subjects with unipolar and bipolar disorders as well as schizophrenia. Therefore, the effects could not be specifically associated with the patients with schizophrenia. Moreover, the meta-analysis indicated there were insufficient data to analyse the effects on negative symptoms and anxiety (Cramer et al., 2016). Only one meta-analysis reported a significant impact of treatment on depressive symptoms (Louise et al., 2018).

Interventions in most of the systematic review and meta-analysis studies included mindfulness-based intervention alone or mindfulness-based intervention combined with others, such as ACT therapy, which may have influenced the effects of mindfulness-based intervention. In these meta-analyses (Cramer et al., 2016; Louise et al., 2018), there was a bias in the data due to inclusion of two studies that used the same dataset (Chien & Lee, 2013; Chien & Thompson, 2014). Overall, these review and meta-analysis studies provide some insights, but the direct effectiveness of mindfulness-based interventions for patients with schizophrenia remains unknown.

Developing mindfulness-based interventions for patients with schizophrenia needs to consider the characteristics of their psychotic symptoms. Some case reports found that meditation in mindful intervention was considered inappropriate for schizophrenic patients by influencing patients' association with psychotic symptoms (Kuijper et al., 2007; Walsh & Roche, 1979). Thus, mindfulness-based intervention was modified with a brief body scan at the beginning followed by a shorter meditation and ensuring clear guidance for patients with schizophrenia (Chadwick, 2006). To understand the effects of mindfulness-based intervention specifically developed for schizophrenic patients, we conducted a meta-analysis to confirm its effects on psychotic symptoms, positive and negative symptoms, and depressive symptoms.

2 | REVIEW

2.1 | Aims

The aims of this meta-analysis are as follows: (a) to evaluate the immediate and follow-up effects of mindfulness-based intervention on psychotic symptoms, positive symptoms, negative symptoms, depressive symptoms, anxiety, and rehospitalization; (b) to identify moderators of mindfulness-based intervention effects on psychotic symptoms; and (c) to provide suggestions for future intervention design.

2.2 | Design

This meta-analysis was performed using the guidelines from the Cochrane Handbook for Systematic Reviews of Intervention (Higgins & Green, 2011) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009).

2.3 | Search methods

Seven databases were searched to find any potentially relevant studies, including Medline (via Ovid), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, CINAHL, National Digital

Library of Theses and Dissertations in Taiwan, and Airiti Library. The search was performed for articles published from the earliest available date to 30 April 2019.

No language limitation was set for the search strategy but only English and Chinese language search terms were used. The following free text and controlled vocabulary were initially searched in Medline (via Ovid): ((schizoaffective or schizophrenia or psychotic or psychosis or paranoi* or delusion* or hallucination* or distressing voices or voice hearing or hearing voice) OR (exp Schizophrenia/ or exp Paranoid Disorders/ or exp Psychotic Disorders/)) AND ((mindfulness or mindfulness-based or MBSR or MBCT).ti,ab. OR (exp Mindfulness/)). Subsequently, the filters to identify RCT, which were recommended by Cochrane, were adopted for advanced searches (Jackson et al., 2009). This search strategy was modified for each of the other six databases. Details of search strategies are presented in Appendix S1.

2.4 | Search outcome

The inclusion criteria were as follows: (a) participants aged 18 years old and above; (b) participants were clinically diagnosed with schizophrenia spectrum disorders; (c) at least one experimental group received mindfulness-based intervention; (d) the control group received treatment as usual/usual care/routine care which is already used in clinical practice; (e) the outcomes of the studies were psychotic symptoms, positive symptoms, negative symptoms, depressive symptoms, anxiety, and/or re-hospitalization; and (f) study design was RCT. The exclusion criteria were as follows: mindfulness was not considered an element of intervention.

Titles and abstracts were screened through searches to reference management software (EndNote X9). After removing duplicate studies, two authors (Liu & Li) independently screened titles and abstracts of all the studies. To confirm the inclusion, full-text publications of eligible studies were retrieved and screened. Reasons for exclusion of publications of eligible studies were recorded. Duplicate publications on selected studies were also examined to determine whether the data from a single trial were published in multiple reports, to decrease publication bias. Once multiple published reports from a single trial were identified, the relevant reported data were treated as a single intervention. The details of the selection process were recorded to generate the PRISMA flow diagram.

2.5 | Quality appraisal

The included studies were subsequently assessed for methodological quality by using the Revised Cochrane 'Risk of bias' tool for randomized trials (RoB 2.0; Higgins et al., 2016). Five potential biases were critically assessed by two authors (Liu & Li), including bias arising from the randomization process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in

measurement of the outcome, and bias in selection of the reported result. The potential bias level of each study was judged as 'high risk', 'low risk', or 'some concerns'. The summarized risk of bias tables was generated using Review Manager (RevMan 5.3).

2.6 | Data abstraction

Two authors performed the data extraction using self-designed data extraction forms. Two randomly selected studies were used to test the appropriateness of the data extraction forms. The forms included the following information: authors, year of publication, country of the participants, study design, characteristics of participants, intervention details, control details, relevant measures and outcomes, and other information (e.g., type of analysis, recruitment rate, retention rate, etc.).

The primary outcomes were psychotic symptoms, positive symptoms, and negative symptoms; and secondary outcomes were depressive symptoms, anxiety, and rehospitalization. Except for rehospitalization data, outcomes were assessed by published psychometric measures.

2.7 | Synthesis

Hedges' g and 95% confidence intervals (CIs), which corrects for biases due to small sample sizes from Cohen's d , were calculated as effect sizes (Hedges et al., 1985). Only the relevant arms were included when multiple arms were presented in a single study. Appropriate data were pooled and meta-analysis performed by using a random-effects model. RevMan 5.3 software was adopted to manage all data and to perform meta-analysis. The primary outcomes were grouped based on the length of follow-up. When studies report more than one time point within the considered time frame, the latest time point which was the closest to the time limit was chosen for analyses. Both immediately post-intervention and short-term follow-up (3- to 6-month post-intervention) outcome data were collected for meta-analysis.

2.7.1 | Heterogeneity analysis

Studies included within each comparison were assessed for clinical heterogeneity in terms of variability in interventions and control status, settings, participants, and results. Forest plots were visually inspected and I^2 statistic and the chi-square test (Q test; Huedo-Medina et al., 2006) were performed to assess heterogeneity. Values over 75% in I^2 statistics, which were suggested as considerable heterogeneity by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011), were the guide used to interpret the results. When forest plots were symmetric, the p -value of Q test $<.05$ and I^2 statistics over 75% would be considered high heterogeneity.

2.7.2 | Assessment of publication biases

Publication bias was visually judged by the funnel plot (Duval & Tweedie, 2000). A symmetric distribution funnel implies no publication bias, whereas an asymmetrical funnel implies potential publication bias of the included studies.

2.7.3 | Sensitivity analysis

Sensitivity analyses (Higgins & Green, 2011) were performed to examine the extent of studies judged as high risk of bias has an impact on results were determined by their removal from the pooled effect sizes. Both random-effects and fixed-effect models were rerun to evaluate how outcomes are affected. A pooled estimated effect size was calculated by removing a study individually for assessment of how each study affects the pooled estimate. No significant difference was found.

2.7.4 | Subgroup analysis

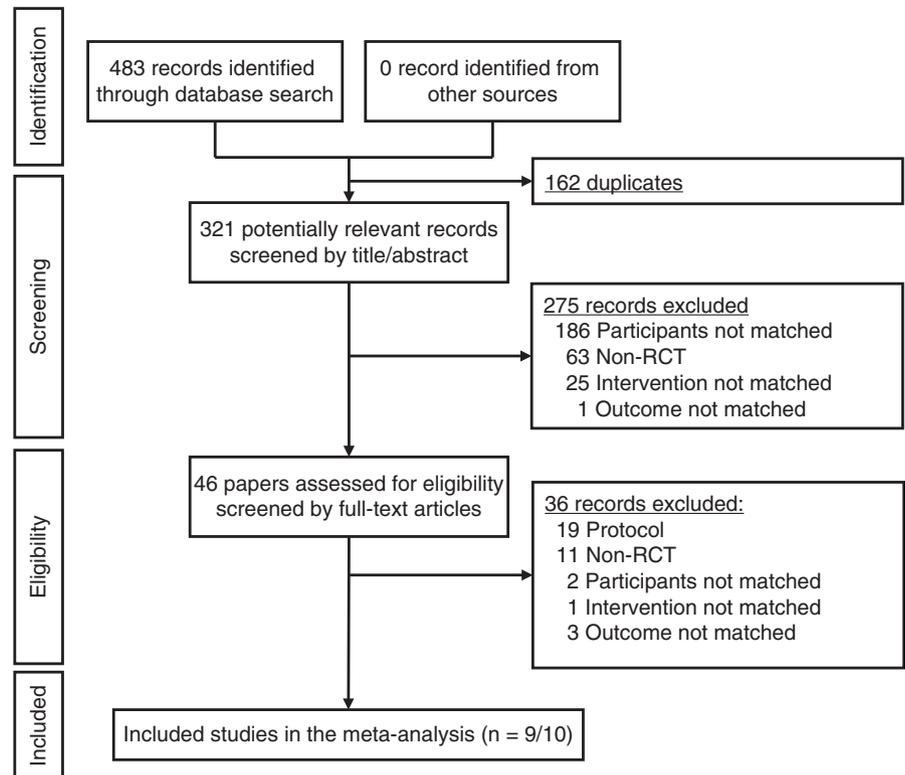
Subgroup analyses were conducted to examine the moderators that will lead to a more remarkable outcome by further calculating the impact of the categorical variables on effect size. The random-effects model was adopted to examine the variables, where a moderator may be recognized when the Q test is significant (Higgins & Green, 2011).

3 | RESULTS

A total of 483 citations were identified from seven databases. After removing 162 duplicates, 321 unique citations were screened out by titles and abstracts. The full-text publications were retrieved for the remaining 46 citations and were assessed for the eligibility criteria. From these full-text studies, 39 citations were excluded with reasons recorded as showed in Figure 1. A total of 10 studies (Chadwick et al., 2009, 2016; Chien et al., 2017; Chien & Lee, 2013; Chien & Thompson, 2014; Langer et al., 2012; Lee, 2019; Lee & Jiang, 2018; Shieh et al., 2018; Wang et al., 2016) were identified by the search. However, a recent systematic review pointed out that the reported data of two studies (Chien & Lee, 2013; Chien & Thompson, 2014) were from the same trial (Aust & Bradshaw, 2017). Therefore, a total of 10 eligible studies reporting data from 9 trials were included in this meta-analysis.

3.1 | Study characteristics

Of the nine RCTs, eight were published in English and one was in Traditional Chinese. The studies were published from 2009 to 2019. For the study design, six studies were two-arm RCTs with inactive-controlled design (Chadwick et al., 2009, 2016; Langer et al., 2012; Lee, 2019; Lee & Jiang, 2018; Shieh et al., 2018) and

FIGURE 1 Flowchart of inclusion and exclusion criteria for meta-analysis

three studies were three-arm RCTs with a parallel conventional psychoeducation group and an inactive controlled design (Chien et al., 2017; Chien & Thompson, 2014; Wang et al., 2016). Six studies were conducted in Chinese countries (Hong Kong and Taiwan; Chien et al., 2017; Chien & Thompson, 2014; Lee, 2019; Lee & Jiang, 2018; Shieh et al., 2018; Wang et al., 2016) and three studies were conducted in Western countries, including England (Chadwick et al., 2009, 2016) and Spain (Langer et al., 2012). The sample sizes in the meta-analysis ranged from 18 to 223 participants. Most of the participants were diagnosed with schizophrenia spectrum disorders by a diagnostic standard, while one study (Shieh et al., 2018) did not provide information for the diagnostic tool. Most participants were in outpatient settings, while three studies in Taiwan were set in the chronic ward (Lee & Jiang, 2018; Shieh et al., 2018) or daycare centre (Lee, 2019). The mean age of the participants in these three Taiwanese studies was 52 years, which was higher than the other six studies, where the mean age ranged from 24 to 42 years.

All mindfulness-based interventions were in a group-based format. There were three major types of mindfulness-based intervention: an 8–12 session person-based cognitive therapy (PBCT; Chadwick et al., 2009, 2016; Langer et al., 2012), a 12 session mindfulness-based psychoeducation group (MBPEG; Chien et al., 2017; Chien & Thompson, 2014; Wang et al., 2016), or 8 sessions of other types (Lee, 2019; Lee & Jiang, 2018; Shieh et al., 2018). PBCT emphasizes there are two times medication practice with <10 min for each time. MBPEG includes education about disease knowledge and management in addition to mindfulness practice. Other types of mindfulness include mindful Yoga. MBPEG was provided by

clinical nurses while other types of mindfulness-based interventions were provided by psychologists. Three studies were conducted in western societies (Chadwick et al., 2009, 2016; Langer et al., 2012), while others were conducted in Chinese societies (Hong Kong and Taiwan). The intervention characteristics are presented in Table 1.

3.2 | Methodological quality

Risk of bias for methodological quality was assessed for each included study. The risk of bias graph and bias summary were produced using RevMan software and presented in Figure 2. In sum, four of nine studies (44%) were judged to be at high risk of bias, three studies (33%) were high risk, and two (22%) were low risk. Furthermore, publication bias was examined by funnel plots. Funnel plots were asymmetric in all outcomes (Appendix S2).

3.3 | Effectiveness of mindfulness-based intervention

The overall immediate post-treatment effects and follow-up effects on primary and secondary outcomes are reported in Table 2.

3.3.1 | Primary outcomes

In the results of patients' psychotic symptoms, five studies that measured immediate postintervention effects and three studies

TABLE 1 Summary of study characteristics

Authors	Country	Design	Population	Time
Chadwick et al. (2009)	England, London	Two-arm RCT	Schizophrenia (DSM-4) Age: >18 y/o (<i>mean</i> = 41.6; <i>SD</i> = 8.1) • Community mental health care	Duration: 10 weeks (5 weeks of intervention plus 5 weeks of home practice) Length: 60 min Frequency: twice weekly Sessions: 10
Chadwick et al. (2016)	England, London	Two-arm RCT	Schizophrenia or schizoaffective disorder Age: 18–65 y/o (<i>median</i> = 42) • Outpatients (two sites)	Duration: NI (max 4M) Length: 90 min Frequency: NI Sessions: 12
Chien and Thompson (2014)	Hong Kong	Three-arm RCT	Schizophrenia (DSM-4) Age: >18 y/o (<i>mean</i> = 25.6) • Outpatient clinics (three sites)	Duration: 24 weeks Length: 120 min Frequency: biweekly Sessions: 12
Chien et al. (2017)	Hong Kong + China + Taiwan	Three-arm RCT	Schizophrenia (DSM-4) or other psychotic disorders (SCID-I) Age: 18–64 y/o (<i>mean</i> = 25.6) • Outpatient clinics (six sites)	Duration: 24 weeks Length: 120 min Frequency: biweekly Sessions: 12
Langer et al. (2012)	Spain, Almeria	Two-arm RCT	Schizophrenia or Schizophrenia form disorder or schizoaffective disorder or delusional disorder (DSM-4-TR) Age: (<i>mean</i> = 34.7; <i>SD</i> = 8.2)	Duration: 8 weeks Length: 60 min Frequency: weekly Sessions: 8

TABLE 1 (Continued)

EG/CG	Measures	Other
EG: PBCT Format: Group-based Homework: practice at home with guided CDs (10-min mindfulness practice plus 3-min breathing meditation) after 5-week intervention Intervener: Researcher (psychology background; 3-year MBCT training) Content: (Chadwick, 2006) Two 10-min mindfulness meditations plus two 15–20-min reflective group discussion for insight per session CG: TAU + Wait-list	Time points: Pre-test; Posttest Measures: Positive Symptom: PSYRATS	Analysis: ITT Recruitment rate: 63% (22/35) Retention rate: -Posttest EG: 82% (9/11) CG: 64% (7/11)
EG: PBCT plus TAU Format: Group Homework: encourage daily practice by using recording (10 min)+record for voice or self Intervener: Researcher (psychology background) with two clinical psychologists as group facilitators Content: (Chadwick, 2006) Ten-minute mindfulness practice combines focused attention on body and breath per sessions. Session 1–3: Draw out voice hearing experience and practice cognitive skill Session 4–6: Explore personal control Session 7–12: Decentralize from negative schemata and build positive schematic beliefs CG: TAU	Time points: Pre-test; Posttest; Six months posttest F/U Measures: Positive Symptom: PSYRATS Depression: HADS-D Anxiety : HADS-A	Analysis: ITT Recruitment rate: 50% (108/214) Retention rate: -Posttest EG: 89% (48/54) CG: 83% (45/54) -F/U EG: 80% (43/54) CG: 72% (39/54)
EG1 MBPEG + TAU Format: Group (11–13) Homework: skill practice daily Intervener: nurse (3-day workshop) Content: Phase I: 1. Orientation; 2. Awareness of body; 3. Empowerment Phase II: 1. Disease knowledge; 2. Management Phase III: 1. Relapse prevention; 2. Future plan EG2 CPEG + TAU Format: Group(11–13) Homework: X Intervener: Psychiatric Nurse (3-day workshop) Content: empowerment; education and survival skill; relapse prevention; evaluation CG: TAU	Time points: Pre-test; Posttest; 12 months posttest F/U; 24 months posttest F/U Measures: Psychotic Symptoms: BPRS Re-hospitalization: Average number and length	Analysis: ITT Recruitment rate: 23.7%(107/450) Retention rate: -Posttest EG1: 92%(33/36) EG2: 92%(33/36) CG: 97%(34/35)
EG1: MBPEG + TAU Format: Group (10–12) Homework: Mindfulness skill practice twice daily Intervener: APN (2–3 years mindfulness training) Content: Three phases design (Similar to Chien & Thompson, 2014) EG 2: CPEG + TAU Format: Group (10–12) Homework: NI Intervener: Psychiatric nurse (3-day training) Content: Joining with patients and families; survival skills; problem-solving training; review CG: TAU	Time points: Pre-test; Posttest; Six months posttest F/U; 12 months posttest F/U; 24 months posttest F/U Measures: Psychotic Symptoms: PANSS Positive Symptoms: PANSS-P Negative Symptoms: PANSS-N Re-hospitalization: Average number and length	Analysis: ITT Recruitment rate: 52% (342/658) Retention rate: -Posttest EG1: 90% (11/114) EG2: 90% (11/114) CG: 91% (10/114) -F/U (24M) EG1: 84% (17/114) EG2: 83% (19/114) CG: 83% (19/114)
EG Format: Group Homework: CD for body scan and meditation Intervener: MBCT therapist (2-year experience) Content: (Chadwick, 2006) Two 10-min mindfulness meditations plus two 15- to 20-min reflective group discussion for insight per session CG: TAU	Time points: Pre-test; Posttest Measures: Psychotic Symptoms: CGI-SCH	Analysis: PP Recruitment rate: X Retention rate: V EG: 64%(7/11) CG: 92%(11/12)

(Continues)

TABLE 1 (Continued)

Authors	Country	Design	Population	Time
Lee (2019)	Taiwan	Two-arm RCT	Schizophrenia spectrum (NI) Age: 18–65 y/o (<i>mean</i> = 52.5) <ul style="list-style-type: none"> • Patients with psychotic symptom were excluded. • Rehabilitation units and daycare centres 	Duration: 8 weeks Length: 90 min Frequency: weekly Sessions: 8
Lee and Jiang (2018)	Taiwan	Two-arm RCT	Schizophrenia (NI) Age: (Overall <i>mean</i> = 52.31) EG-M = 48.97 CG-M = 4.43 <ul style="list-style-type: none"> • Chronic wards 	Duration: 8 weeks Length: 90 min Frequency: weekly Sessions: 8
Shieh et al. (2018)	Taiwan	Two-arm RCT	Schizophrenia (NI) Age: (<i>mean</i> = 51.75; <i>SD</i> = 8.13) <ul style="list-style-type: none"> • Inpatients of Chronic units 	Duration: 8 weeks Length: 90 min Frequency: weekly Sessions: 8
Wang et al. (2016)	Hong Kong	Three-arm RCT	Schizophrenia spectrum disorder (DSM-4-TR) Age: 18–60 y/o (<i>mean</i> = 24.3) <ul style="list-style-type: none"> • Outpatient clinics (three sites) 	Duration: 24 weeks Length: 120 min Frequency: biweekly Sessions: 12

Note: BDI-II, Beck Depression Inventory-II; BPRS, Brief Psychiatric Rating Scale; CG, control group; CGI-SCH, Clinical Global Impression–Schizophrenia Scale; CMV, Chinese Mandarin version; CPEG, conventional psychoeducation group; DSM, The Diagnostic and Statistical Manual of Mental Disorders; EG, experiment group; F/U, follow-up; HADS, Hospital Anxiety Depression Scale, HADS-A, Anxiety subscale of HADS; HADS-D, Depression subscale of HADS; ITT, intended to treat; M, mean; MBI, mindfulness-based intervention; MblfS, mindfulness-based intervention for chronic Schizophrenia; MBPEG, mindfulness-based psychoeducation group; MBT, mindfulness-based training; MPPG, mindfulness-based psychoeducation group program; NI, no information; PANSS, Positive and Negative Syndrome Scale; PANSS-N, Negative Syndrome subscale of PANSS; PANSS-P, Positive Syndrome subscale of PANSS; PBCT, Person-Based Cognitive Therapy; PP, per protocol; PSYRATS, Psychiatric Symptom Rating Scale; SANS, Scale for Assessment of Negative Symptoms; S-ART, self-awareness, self-regulation, and self-transcendence; SD, standard deviation; TAU, treat as usual.

TABLE 1 (Continued)

EG/CG	Measures	Other
<p>EG: MBI based on S-ART Format: Group Homework: daily practice Intervener: six clinical psychologists (3-d MBI training) Content: introduction; breath meditation; mindfully writing; mindfully eat; mindfully read; mindfully stretch; self-compassionate meditation CG: TAU</p>	<p>Time points: Pre-test; Posttest; 3 months posttest F/U Measures: Psychotic Symptoms: CMV-PANSS Positive Symptoms: CMV-PANSS-P Negative Symptoms: CMV-PANSS-N Depression: BDI-II</p>	<p>Analysis: ITT Recruitment rate: NI Retention rate: -Posttest & F/U EG:67%(20/30) CG:100%(0/30)</p>
<p>EG: MbIfS Format: Group Homework: NI Intervener: NI Content: Auto-Pilot; Curiosity; Focus on the Present; Eating; Concentration; Mindfully Act; Mindful Yoga; Balanced Lifestyle CG: TAU</p>	<p>Time points: Pre-test; Posttest; 3 months posttest F/U Measures: Negative Symptoms: SANS Depression: BDI-II</p>	<p>Analysis: PP Recruitment rate: NI Retention rate: -Posttest & F/U EG:63%(19/30) CG:100%(30/30)</p>
<p>EG: MBT Format: Group Homework: Assigned Intervener: Clinical psychologists (trained by experienced mindfulness teacher) Content: Auto-Pilot; Curiosity; Focus on the Present; Eating; Concentration; Mindfully Act; Mindful Yoga; Balanced Lifestyle CG: TAU</p>	<p>Time points: Pre-test; Posttest; 3 months posttest F/U Measures: Positive Symptoms: PANSS-P Negative Symptoms: PANSS-N</p>	<p>Analysis: PP Recruitment rate: NI Retention rate: -Posttest & F/U EG:70%(21/30) CG:100%(30/30)</p>
<p>EG1 MPGP Format: group Homework: Assigned Intervener: psychiatric APN (3-year mindfulness group experience) Content: 1. Program overview and engagement 2. Enhancing awareness of bodily sensations, thoughts, and feelings regarding illness 3. Guided body awareness and mindful exercises and homework practices 4. Education of illness management 5. Encountering with and controlling negative thoughts, and life difficulties caused by symptoms, and practicing problem-solving strategies 6. Behavioural rehearsals of means for relapse prevention 7. Mindfulness practices and realistic future plans EG2 CPEG Format: Group Homework: NI Intervener: (training) Content: Joining with patients and families; survival skills; problem-solving training; review CG: TAU</p>	<p>Time points: Pre-test; Posttest; 6 months posttest F/U Measures: Psychotic Symptoms: PANSS Positive Symptoms: PANSS-P Negative Symptoms: PANSS-N Re-hospitalization: Average number and length</p>	<p>Analysis: ITT Recruitment rate: 57%(340/600) Retention rate: -Posttest EG1:89%(41/46) EG2:87%(41/46) CG:93%(43/46) -F/U EG1:91%(42/46) EG2:87%(40/46) CG:87%(40/46)</p>

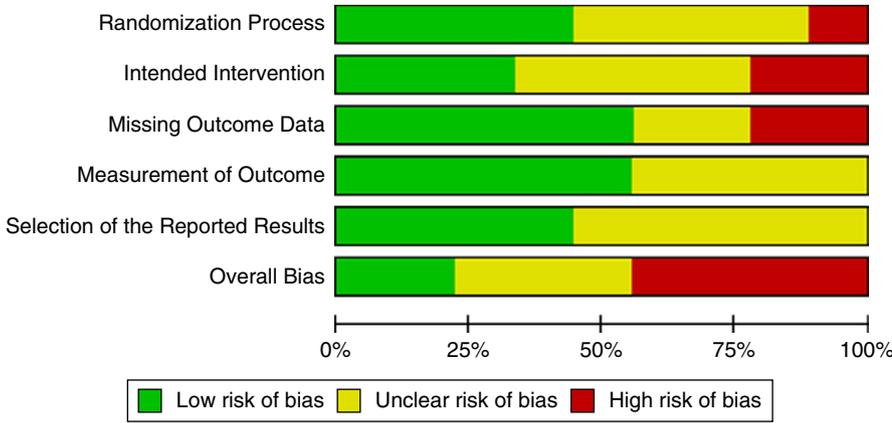


FIGURE 2 (a) Risk of bias graph; (b) Risk of bias summary

	Randomization Process	Intended Intervention	Missing Outcome Data	Measurement of Outcome	Selection of the Reported Results	Overall Bias
Chadwick et al. (2009)	+	?	+	?	?	?
Chadwick et al. (2016)	+	?	+	+	+	?
Chien et al. (2014)	?	+	+	+	+	?
Chien et al. (2017)	+	+	+	+	+	+
Langer et al. (2012)	?	?	-	+	?	-
Lee (2019)	-	?	-	?	?	-
Lee et al. (2018)	?	-	?	?	?	-
Shieh et al. (2018)	?	-	?	?	?	-
Wang et al. (2016)	+	+	+	+	+	+

that measured follow-up effects within 3–6 months postintervention were included in this meta-analysis. The results (Appendix S3) showed that mindfulness-based intervention had a moderate-to-high immediate effect on psychotic symptoms with a *g*-value of -0.79 (95% CI = -0.98 to -0.59 , $p < .01$). These studies were found to have low heterogeneity ($Q = 1.88$, $p = .76$, $I^2 = 0\%$). No significant follow-up effects were found ($g = -0.49$, 95% CI = -2.88 to 1.91 , $p = .69$).

In the results of patients' positive symptoms, six studies that measured the immediate postintervention effects and five studies that measured follow-up effects were included. The results showed that mindfulness-based intervention had a small-to-moderate immediate effect on positive symptoms with a *g*-value of -0.31 (95%

CI = -0.54 to -0.07 , $p = .01$). These studies were found to be low heterogeneity ($Q = 7.75$, $p = .17$, $I^2 = 36\%$). No significant follow-up effects were found ($g = -0.33$, 95% CI = -0.99 to 0.33 , $p = .33$).

In the results of patients' negative symptoms, five studies that measured both immediate postintervention effects and follow-up effects were included. The results showed that mindfulness-based intervention had a moderate immediate effect on negative symptoms with a *g*-value of -0.53 (95% CI = -0.72 to -0.35 , $p < .01$). Furthermore, moderate follow-up effects on negative symptoms were found ($g = -0.59$, 95% CI = -0.78 to -0.41 , $p < .01$). These studies were found to be low heterogeneity (Immediate effects: $Q = 2.40$, $p = .66$, $I^2 = 0\%$; Follow-up effects: $Q = 2.06$, $p = .73$, $I^2 = 0\%$).

TABLE 2 Summary of overall immediate postintervention effects and short-term follow-up effects

	k	Participants		Effect size		Heterogeneity	
		N	g	95% CI	Q	I ²	
Immediate postintervention							
Psychotic symptoms	5	449	-0.79***	(-0.98, -0.59)	1.88	0	
Positive symptoms	6	537	-0.31*	(-0.54, -0.07)	7.75	36	
Negative symptoms	5	460	-0.53***	(-0.72, -0.35)	2.40	0	
Depression	3	207	-0.28*	(-0.56, -0.00)	0.59	0	
Anxiety	1	108	-0.71	(-2.21, 0.79)	-	-	
Re-hospitalization (average times)	3	381	-0.24 [†]	(-0.49, 0.01)	0.15	0	
Re-hospitalization (days of duration)	3	381	-4.95*** [†]	(-6.51, -3.39)	2.45	18	
Short-term follow-up							
Psychotic symptoms	3	360	-0.49	(-2.88, 1.91)	121.00***	98	
Positive symptoms	5	519	-0.33	(-0.99, 0.33)	48.52***	92	
Negative symptoms	5	460	-0.59***	(-0.78, -0.41)	2.06	0	

Note: k, number of studies; N, number of participants; [†]mean differences; * $p < .05$; ** $p < .01$; *** $p < .001$

3.3.2 | Secondary outcomes

In the results of patients' depressive symptoms, three studies measured the postintervention effects and the results showed that mindfulness-based intervention had a small-to-moderate immediate effect on depressive symptoms ($g = -0.28$, 95% CI = -0.56 to -0.00 , $p < .05$). Only one study examined the effects on anxiety and no statistical significance was found.

In the results of rehospitalization-related outcomes, three studies examined the effects of mindfulness-based intervention on the average times and days of duration. The results showed that mindfulness-based intervention could result in a reduction of 4.95 days of rehospitalization (95% CI = -6.51 to -3.39 , $p < .01$) in contrast to control group. These studies were found to be low heterogeneity ($Q = 2.45$, $p = .29$, $I^2 = 18\%$). No significant effects on average times of rehospitalization were found.

3.3.3 | Subgroup analysis

The moderating effects of mindfulness-based intervention on psychotic symptoms, positive symptoms, and negative symptoms as the primary outcomes were further examined for moderating effects by using subgroup analysis. Because of the limited number of studies for each outcome and the low heterogeneity in each result, only the moderating effects of intervention type and intervention provider were examined. The moderating effect of the three intervention types were examined and no significant differences between subgroups were found on three primary outcomes. The moderating effects of intervention provider were found on positive symptoms, the nurse-led mindfulness-based intervention ($g = -0.54$,

95% CI = -0.87 to -0.21 , $p < .01$) evidenced significantly higher effect size than psychologist-led mindfulness-based intervention ($g = -0.09$, 95% CI = -0.36 to 0.17 , $p = .49$), with a Q-value of 4.25 ($p < .05$). The moderating effects were not found on psychotic or negative symptoms (Table 3).

4 | DISCUSSION

In this current meta-analysis of nine RCTs, beneficial immediate postintervention effects of mindfulness-based intervention were identified for psychotic symptoms, positive symptoms, negative symptoms, depressive symptoms, and the duration of rehospitalization in patients with schizophrenia compared with control. A small-to-moderate immediate postintervention effect on positive symptoms was found. This finding was in contrast to a previous meta-analysis that found mindfulness-based intervention failed to decrease the positive symptoms (Cramer et al., 2016). This current meta-analysis provided stronger evidence by including five more RCTs that evaluated positive symptoms. Four theoretical mechanisms were proposed by Strauss et al. (2015): (a) mindful observation may protect against preoccupation with symptoms; (b) acceptance presents an alternative to experiential avoidance or suppression; (c) a decentred awareness may reduce the impact of negative voice-content and self-beliefs on distress; and (d) reducing of control behaviours, such as rumination and worry. Most included studies (Chadwick et al., 2009; Chien et al., 2017; Chien & Lee, 2013; Chien & Thompson, 2014; Lee & Jiang, 2018; Shieh et al., 2018) explained the mechanisms of mindfulness practice improving the positive symptoms (delusion and hallucination). They demonstrate that mindfulness practice helped schizophrenia

TABLE 3 Subgroup analysis of immediate postintervention effects on psychotic symptoms, positive symptoms, and negative symptoms

	k	Participants		Effect size		Heterogeneity	
		N	g	95% CI	Q	I ²	
Psychotic symptoms							
Intervention designs						0.19	0
MBPEG	3	381	-0.80***	(-1.01, -0.59)	1.68	0	0
PBCT	1	18	-0.63	(-1.60, 0.35)	-	0	0
Others	1	50	-0.71*	(-1.30, -0.13)	-	36	0
Intervention providers						0.17	0
Nurse led	3	381	-0.80***	(-1.01, -0.59)	1.68	0	0
Psychologist led	2	68	-0.69***	(-1.19, -0.19)	0.02	0	0
Positive symptoms							
Intervention designs						4.48	55.3
MBPEG	2	310	-0.54***	(-0.87, -0.21)	1.82	45	0
PBCT	2	126	-0.04	(-0.39, 0.31)	0.13	0	0
Others	2	101	-0.17	(-0.56, 0.23)	0.21	0	0
Intervention providers						4.25*	76.5
Nurse led	2	310	-0.54***	(-0.87, -0.21)	1.82	45	0
Psychologist led	4	227	-0.09	(-0.36, 0.17)	0.56	0	0
Negative symptoms							
Intervention designs						2.27	55.9
MBPEG	2	310	-0.44	(-0.66, -0.21)	0.03	0	0
Others	3	150	-0.75	(-1.09, -0.41)	0.09	0	0
Intervention providers						2.27	55.9
Nurse led	2	310	-0.44	(-0.66, -0.21)	0.03	0	0
Psychologist led	3	150	-0.75	(-1.09, -0.41)	0.09	0	0

Note: k, number of studies; N, number of participants; MBPEG, mindfulness-based psychoeducation group; PBCT, person-based cognitive therapy; Others: including mindfulness-based intervention for chronic Schizophrenia (MblfS), mindfulness-based training (MBT), and Mindfulness based on self-awareness, self-regulation, and self-transcendence (S-ART); * $p < .05$; ** $p < .01$; *** $p < .001$.

patients to be aware of the present moment at their daily life and by this training, they could let go of rumination of symptom distress and controlling the unwanted voices and then accept psychotic experience. Mindfulness practice enhances patients' metacognitive skills such as interoceptive awareness and subsequently reduces their habitual belief in the negative consequences of psychotic symptoms such as voice omnipotence (Chadwick, 2006). The positive emotional experiences such as feeling calm and peaceful after mindfulness practice could also reduce the impacts of emotional distress on triggering the positive symptoms (Shieh et al., 2018). Wang et al. (2016) proposed top-down and bottom-up mechanisms of cognitive remediation after mindfulness intervention. Top-down mechanism demonstrates mindfulness enhancing interoceptive attention to bodily sensations and through this interoceptive attention networks increasing and changing information processing in the brain, a more normal perceptual experience and cortical activity are increased. Bottom-up mechanism demonstrates mindfulness intervention that enhances the modulation of emotion-generative brain regions (limbic) without involving the cognitive regulation such as appraisal and suppression in frontal regions.

Moderate-to-larger effects were found in reduction in negative symptoms both immediately postintervention and at short-term follow-up. This meta-analysis is the first identification and examination of the sustaining effects of negative symptoms. Mindfulness practice includes mindfulness reading, mindfulness breathing, and loving kindness meditation for others and for themselves in their daily life (Lee, 2019). Negative symptoms of avolition and affective flattening could be attenuated by the mindfulness practice because patients could concentrate and reengage in their here-and-now daily life activities and have the chance to share their feeling with others (Chien & Thompson, 2014; Lee, 2019; Lee & Jiang, 2018). Moreover, participating mindfulness intervention in group format intervention provides patients the chance to go outside and interact with others. Mindfulness intervention enhancing schizophrenia patients' emotional regulation and positive feelings to others could decrease the negative symptoms of anhedonia and limited emotional expression (Chien & Thompson, 2014; Lee & Jiang, 2018; Shieh et al., 2018).

Furthermore, according to subgroup analysis, we identified the nurse-led mindfulness-based intervention was an important moderator on decreasing positive symptoms. This might be explained

by several reasons. First, the nurse-led interventions were longer than psychologist-led interventions. Mindfulness is a cognitive behaviour skill which is expected to require time to learn, practice and achieve positive changes, so longer sessions and more of them could increase the benefits. Second, those nurse-led interventions designed by Chien and team and incorporated psychoeducational topics of disease knowledge, symptoms management, and relapse prevention. Combining mindfulness practice and psychoeducation might be beneficial to decrease positive symptoms of patients. Third, the author further examined the retention rate and found that the nurse-led interventions had higher retention rate than the others. This might be explained by therapeutic alliance which might have a causal effect on psychosis of a psychological intervention (Goldsmith et al., 2015). Nurses are the main care providers and therefore highly trusted by patients, which might make it easier to build a therapeutic alliance. Fourth, the author further examined the composition of participants and found the participants of nurse-led interventions were all Chinese patients. The previous meta-analysis of the other third-wave CBT confirmed that cultural differences are an important moderator of effects on delusions (Liu et al., 2018). Chinese participants might get the habit of better adherence to the instruction or have more interest in the mindfulness skills (Ainley, 2006).

Studies analysed here were mainly of outpatient participants, although three Taiwanese studies evaluated inpatients and patients at a daycare centre. Although this difference in settings might be expected to also reflect differences in symptom severity, no significant differences in effects were seen between these Taiwanese studies and the others. Inpatient or daycare participants were relatively more stable than patients in acute settings. However, no existing RCTs of mindfulness-based intervention were conducted in acute clinical settings. Furthermore, this meta-analysis found the intervention might decrease rehospitalization duration by almost 5 days compared with routine care, indicating that mindfulness-based intervention can be cost effective. However, only few studies took cost-related outcomes into consideration. Thus, the authors call for further studies to be conducted in different clinical settings, with a wider range of symptom severity of patients and with measurement of cost-related outcomes included as references for stakeholders, to maximize utility of the studies for decision-making.

Although the effectiveness of group format mindfulness-based interventions on psychotic symptoms was identified in this current meta-analysis, these populations were mainly outpatient or from chronic wards and day care centres and the mean ages were relatively young. Whether this type of intervention remains effective in an individual format, with older patients and/or in the setting of an acute ward needs to be examined by future studies.

4.1 | Limitations

The long-term (>6 months) follow-up effects of mindfulness-based intervention for patients with schizophrenia failed to be established

in this meta-analysis since insufficient data were obtained. More studies with a long-term follow-up design are needed for identifying potential sustained effects. As the lack of heterogeneity in resources of participants, intervention delivery, intervention format, and different intervention duration, detailed guidelines could not be established in this meta-analysis. Further diversity intervention designs need to be studied in different clinical settings and different severity of patients with schizophrenia.

5 | CONCLUSION

This meta-analysis identified immediate and short-term benefits of mindfulness-based interventions for patients with schizophrenia. Interventions may be more beneficial if they are nurse-led, long-term, and incorporate psychoeducational material in the intervention design. Thus, mindfulness-based intervention is recommended to advanced practice nurses as a complementary therapy for managing psychotic and depressive symptoms among patients with schizophrenia.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Liu, Li, & Hsiao: Made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; Liu & Hsiao: Involved in drafting the manuscript or revising it critically for important intellectual content; Liu, Li, & Hsiao: Given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; Liu, Li, & Hsiao: Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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