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Targeting relapse prevention and positive symptom in first-episode schizophrenia using brief cognitive behavioral therapy: A pilot randomized controlled study

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ABSTRACT

The present study aimed to provide preliminary evaluation of the effectiveness of a brief CBT intervention focusing on relapse prevention and positive symptom in a Chinese first episode schizophrenia (FES) population. This randomized controlled trial recruited eighty outpatients with FES (as determined using the DSM-IV), aged 16–45 years, and on a current atypical antipsychotic. Patients were randomized to either 10 sessions of individual CBT (intervention group) adjunctive to treatment as usual (TAU) or TAU alone (control group). Outcome assessment of symptoms, relapse, hospitalization, insight and social functioning were administered at baseline and then post treatment (10 weeks), and at 6-month and 12-month follow ups. At 12 months, patients in the intervention group had significantly greater improvements in positive symptoms, general psychopathology and social functioning, as well as significantly lower rates of relapse, compared to the control group. Although patients in both groups demonstrated significantly improved negative symptom and insight scores from baseline, no group differences were found.

This RCT demonstrates that FES patient can greatly benefit from CBT designed to target relapse prevention and positive symptom, with improvements sustained for 1 year following treatment.

1. Introduction

Schizophrenia has become the eighth leading cause of disability world-wide for people aged between 15–44 years (World Health Organization, 2001). It is of vital important that individuals having their first episode of schizophrenia receive adequate treatment (Zhu et al., 2017), as meta-analyses suggest that a long duration of untreated psychosis is associated with worse clinical treatment outcomes, such as more severe symptoms, worse social functioning, and failure to achieve remission (Perkins et al., 2005; Perkins et al., 2004). Although patients with first episode schizophrenia (FES) usually respond well to antipsychotic treatment – potentially due to lower frequency of negative symptoms and better cognition function compared to patients with chronic schizophrenia - they may still experience difficulties with social interaction and stigma, may discontinue treatment (Ohlsen et al., 2004), and may relapse. Even with antipsychotic treatment, relapse rates are 70–80% over the 5 years following first onset and 33% of patients experience relapse at one year follow up (Robinson et al., 2005; Üçok et al., 2006). Relapse prevention is important in FES, as each relapse increases the risk of positive symptoms becoming persistent (Wiersma et al., 1998). Thus, previous studies have suggested combining antipsychotic treatment with psychosocial interventions such as CBT for people with early psychosis and schizophrenia (Alvarez-Jiménez et al., 2009; Penn et al., 2005).

Several meta-analyses and reviews have concluded that CBT is an effective intervention for positive, negative and general symptoms, insight, relapse and social functioning in chronic psychosis patients (Wykes et al., 2008; Zimmermann et al., 2005); however, the picture is less clear for first-episode schizophrenia patients. Of the controlled studies that exist, many report inconsistent findings (Drury et al., 1996, 2000; Garety et al., 2008; Grawe et al., 2006; Haddock et al., 1999b; Jackson et al., 1998, 2008; Jolley et al., 2003; Lewis et al., 2002), with

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issues regarding small sample size (Haddock et al., 1999b; Jackson et al., 1998; Jolley et al., 2003), variable additional treatment, and highly heterogeneous samples (Drury et al., 1996, 2000; Lewis et al., 2002). Importantly, two systematic reviews (Morrison, 2009; Penn et al., 2005) of CBT for first episode psychosis (FEP) concluded that there was limited evidence of significant improvements in symptoms (auditory hallucinations and hopelessness), recovery and functioning, as well as reducing rates of relapse or hospital readmission for first-episode patients given CBT intervention.

Few previous FEP studies have specifically looked at using CBT to target relapse prevention, while studies in chronic patients have demonstrated that CBT focused on relapse prevention is effective in reducing relapse rates. For example, Gumley et al. (2003) found that relapse prevention focused CBT greatly reduced hospital admission and relapse rates in patients with chronic schizophrenia, as well as significantly improving symptoms, global psychopathology and social functioning. This study emphasized the importance of early relapse indicators, which can trigger negative beliefs about relapse and hospitalization. However, a study of relapse prevention therapy (combing individual and family CBT therapy) in early psychosis patients (Gleeson et al., 2009) found that while this was indeed effective in reducing relapse rates over 7 months follow up, this did not generalize to other outcomes, with no improvement in medication adherence, psychosocial functioning or quality of life. Thus, the authors suggested that focusing on relapse prevention alone was not enough, and further consideration of the relevant targets for early CBT interventions is required.

Positive symptoms, such as paranoia, hallucinations and delusions, are stronger predictors of relapse than negative symptom (Lavretsky, 2008; Patel et al., 2014). A recent study in which CBT primarily targeted negative symptoms in schizophrenia patients found that this approach effectively reduced negative symptoms, but nearly 30% patients in the CBT group and 35.1% patients in the cognitive remediation group were readmitted to hospital within 1 year following treatment (Klingberg et al., 2011). Similarly, Jackson et al. (1998) found that while CBT significantly improved negative symptoms in FEP, no group differences were found for rates of relapse and hospitalization. Therefore, the CBT model may need to be modified to provide effective treatment for reducing both positive symptoms and preventing relapse in first episode psychosis.

There is a great need for research investigating CBT for FES across diverse ethnic backgrounds, especially in developing countries (Pontes et al., 2013), with very few studies investigating the effects of CBT in FES in China (Wang et al., 2003). One reason for this is the limited mental health services in China which create a barrier for conducting psychological interventions of long duration for large groups of patients (Chen et al., 2018a,b). Due to this limitation and considering the heightened need for cost-effective treatments in most developing countries (Saraceno et al., 2007), the current study examines a brief CBT intervention rather than costly multimodal treatment.

The aim of this randomized controlled trial was to investigate the effectiveness of a brief CBT intervention designed specifically to target relapse prevention and positive symptom in a Chinese first episode schizophrenia population. The primary outcomes were relapse and hospitalization rates over 12 months, and change in psychotic symptoms from baseline to month 12. The secondary outcomes were changes in insight, social functioning, and occupational functioning from baseline to month 12. We hypothesized that brief CBT intervention would have better positive symptom reduction and lower relapse rates compared to the treatment as usual condition.

2. Methods

2.1. Sampling and study design

Participants were recruited from Beijing Anding Hospital affiliated Capital Medical University between June 2012 and March 2014. Outpatients were referred to this program by psychiatrists. Inclusion criteria were: (1) A diagnosis of schizophrenia as assessed by experienced research psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version; (2) Age between 16–45 years; (3) The current illness episode was their first episode of schizophrenia, and any continuous treatment had been for less than 1 month or was inadequate treatment of less than 3 months verified through clinical interview and medical chart review; (4) Use of a single atypical antipsychotic drug for at least two weeks; (5) A score of 4 or more on the delusion (P1) or hallucination (P3) symptom scales of the Positive and Negative Syndrome Scale (PANSS); (6) Their first psychotic symptoms had occured less than 3 years ago. Exclusion criteria were: (1) Co-morbid diagnosis of mental disability or primary substance dependence; (2) Inability to communicate, or lack of spontaneity and flow of conversation (5 or above on PANSS in conceptual disorganization); (3) Electroconvulsive therapy within the 1 month prior to entry into the study; (4) Serious or unstable physical health condition; (5) Currently receiving any other form of systematic psychotherapy.

Eighty patients met the criteria and were included in the trial. Fig. 1 provides a CONSORT diagram illustrating the flow of participants through the study.

This study was approved by the Human Research and Ethics Committee of Beijing Anding Hospital, Capital Medicine University. Informed consent was obtained from the patients and guardians. This clinical trial is registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-13003929).

2.2. Assessment

Face-to-face assessments of all participants were performed by three clinicians who were blind to the treatment condition, during treatment as usual sessions. The clinicians were trained once every two months and reviewed the standards of the scales, to ensure assessment accuracy and consistency. At baseline and weeks 10, 36 and 62, severity of psychopathology, relapse, number of hospital admissions, insight, and social functioning, were assessed, based on the following guidelines:

Severity of psychopathology was assessed according to the Chinese version of the PANSS (Kay et al., 1987; Tianmei et al., 2004). The Chinese version of this scale has shown good reliability (Cronbach's a = 0.871). It also has a good level of construct validity, with total variance explaining 59% of the variance in symptoms in Chinese patients with schizophrenia (Tianmei et al., 2004). This scale includes 30 items, each of which is scored on a seven-point Likert scale (1 = absence of psychopathology; 7 = very severe symptom). PANSS scores were calculated using three dimensions: positive symptoms, negative symptoms, and general psychopathology.

The Psychotic Symptoms Rating Scale (PSYRATS) is an 11-item rating scale with good validity in schizophrenia patients which evaluates the severity of different dimensions of the psychotic symptoms. The Chinese version of PSYRAT has good reliability (Cronbach's a = 0.943) and validity. The correlation of auditory hallucination, delusion and total scores of the PSYRAT with hallucination, delusion and positive subscale of PANSS is reported to be 0.909, 0.833 and 0.737 respectively (Xu et al., 2012). The items include the frequency, duration, controllability, location, loudness; severity and intensity of stress; amount and degree of negative content; and beliefs about the origin of voices and disruption (Haddock et al., 1999a).

The criteria for relapse was deterioration in regards to worsened psychotic symptoms, as identified by either a rating of 6 or 7 on PANSS thought-disorder items (P2, P3, P5 and G9) OR two or more of these

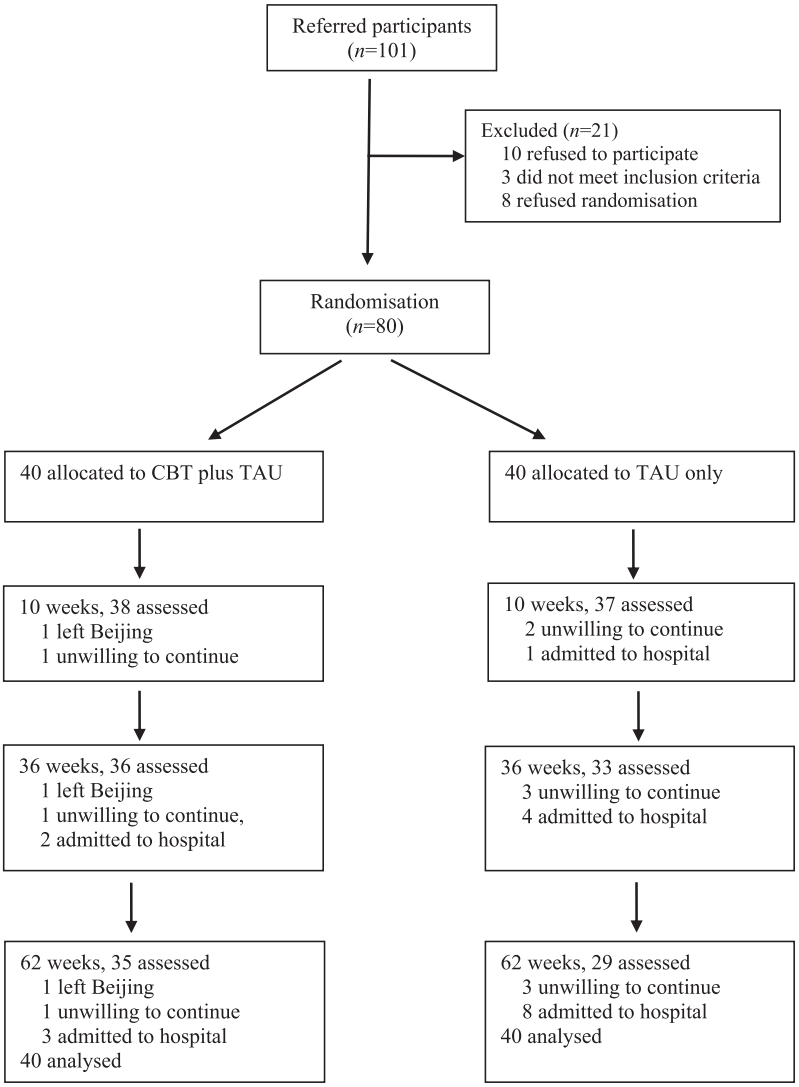

Fig. 1. . CONSORT (Consolidated Standards of Reporting Trials) diagram
CBT, Cognitive-behavioural therapy; TAU, Treatment as usual.

items rating as 5 or above.

Insight was assessed using the Schedule for Assessing Insight (David, 1990). The SAI comprises of questions to assess three dimensions of insight: awareness, relabeling of symptoms, and attitudes to treatment. The SAI includes seven items, each of which is scored on a three-point Likert scale from 0 (no insight) to 2 (good insight). The range of total score is from 0 to 14. The Chinese version of SAI has been demonstrated with good psychometric properties (Xu et al., 2013): the internal consistency of the total scale was high, with Cronbach's α of 0.890 and correlation of the SAI with insight of the PANSS was −0.635.

Social functioning was rated using the Chinese version of the Personal and Social Performance Scale (PSP).The Chinese version of PSP shows good internal consistency (Cronbach's a = 0.840) and construct validity, with statistically significant correlations with the Global Assessment of Functioning scale (Tianmei et al., 2011). The PSP is comprised of four areas of functioning for patients with schizophrenia: (1) participation in socially useful activities; (2) personal and social relationships; (3) self-care; (4) interruptive or aggressive behaviour. Each area of functioning is rated on a six-point Likert scale based on the degree of difficulties ranging from 0 (absence of difficulty) to 6 (severe difficulty).

At week 62 follow-up assessment, participants were evaluated on their employment status and any relapse or hospitalization by a combination of participant interview and review of medical records.

2.3. Procedure

Participants were randomly allocated to the CBT + TAU group or the TAU group (1:1 randomization) after providing informed consent and completing baseline assessments. Randomization was conducted by computer-generated (SPSS Version 20.0) blocks of four random numbers using 1:1 assignment ratio to allocate eligible participants to either of the two groups. Randomization was conducted by a researcher who was not involved in the study. The outcome measures were evaluated by clinicians blind to the study protocol and treatment assignment.

2.4. Treatment group

The brief CBT programme was a manualised individual treatment comprising ten sessions over 10 weeks, with each session typically lasting 45 min. In weeks 1–2, there were 2 sessions per week; in weeks 3–6, there was 1 session per week; in weeks 7–10, there was 1 session per fortnight. The manual was developed based on Turkington et al. (2002) and Wright (2009) and tailored to Chinese patients with first episode schizophrenia. The main goals of this intervention were to apply the general principles of CBT, such as case

formulation, goal setting, homework and the cognitive process and behavior experiment, with a focus on treatment of relapse prevention and primary positive symptoms.

The intervention can be divided into three stages. In the first stage, therapists built a good rapport with patients, assessed patients' life experiences, and developed patients' problem list. In the intermediate stage, patients primarily learnt how to manage positive symptoms (such as delusions, hallucinations, thought disorder) via behavioural experiments, graded exposure, reattribution of symptoms and coping strategies. Emotional problems were also discussed. In the last stage, therapists focused on stress management, problem solving and medication adherence, as well as relapse prevention. Patients in stress management sessions discussed predisposing factors, stressors (e.g. sleep deprivation, trauma and posttraumatic stress symptom), protective factors (e.g. social skills, social support and help seeking) and risk factors (e.g. social isolation, substance abuse). In relapse prevention sessions, patients learned: 1) 6 stages of relapse (quiet period, stress period, hopeless period, loss of control period, mental confusion and psychotic symptom occurrence); 2) the early signs of relapse; 3) how to make their own list of signs of relapse with unique features; 4) how to monitor their symptoms in daily life; 5) how to make emergency plans for early warning signs including grading signs, prevention strategies and plans for seeking help. At the beginning of each session, therapists reviewed patients' homework to ensure patients had mastered the skills covered in previous sessions.

In addition, all participants received treatment as usual; patients were seen monthly by a psychiatrist across the duration of the trial.

2.4.1. Therapists and fidelity

Four therapists provided CBT for the treatment group. All four clinical psychologists held master's degrees in Clinical Psychology with 5–20 years' experience using psychotherapy in hospitals on psychiatric patients with mental disorder. They had been trained in the application of cognitive therapy for psychosis by experienced cognitive–behavioral therapists and received over 200 h of supervision each.

During the study, therapists were supervised in two ways: peer supervision and expert supervision. During peer supervision, therapists presented the case formulation, treatment plan and therapy progress for every case during the first six sessions, and peer therapists provided feedback and suggestions. Therapists then submitted written case reports, case formulations, treatment plans, therapy processes and team members' questions arising from the peer supervision sessions to two experts for supervision. Expert supervision was delivered once every 2 weeks face-to-face. Another expert therapist in CBT for psychosis from the UK was invited to provide supervision via phone, Skype or email on a monthly basis. During supervision, compliance with the manual was also checked by experts to ensure the fidelity of therapy.

2.5. Treatment as usual (TAU)

TAU included medication and case management (including some psychological health education and social support). Psychiatrists evaluated all patients and formulated appropriate drug treatment, and saw patients and their family members in the outpatient unit each month, in order to supervise and encourage medication adherence and provide guidance to family members on managing adverse drug reactions. When patients presented with impulsiveness or serious adverse drug reactions, psychiatrists initiated an emergency response mechanism.

2.6. Medication treatment

Medication prescription was not affected by the trial protocol. The patients in both groups remained under their usual psychiatric care. Medication decisions were made by their primary treating team based on clinical needs. The doses of antipsychotic medication were recorded and converted into equivalent doses of chlorpromazine (Table 3).

2.7. Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS) Version 20.0. The demographic and baseline characteristics of the two groups were compared using independent-sample *t*-test, Mann-Whitney U test or Chi-square test depending on the nature (continuous/ dichotomous, normal distribution/skewed distribution) of those variables. Due to the small sample size, analysis of the outcome measures followed an intention-to-treat (ITT) framework. Regardless of study completing, all cases were included in the statistical analysis of the curative effect, and the last observation carried forward (LOCF) method was used to handle the missing data. If the outcome data indicated a skewed distribution, reciprocal transformation was used. The four time periods were treated as a four-level repeated measure in ANOVA analysis comparing both groups. Main effects of intervention group, time and the interaction between treatment group and time were also estimated (post-hoc comparison). All tests were two-tailed with α set at 0.05. Zero-inflated passion models were used to compare count data on hospitalization and relapse between groups. Kaplan-Meier survival analyses were used to calculate the estimated time from baseline to response and relapse. The analyses included patients who met the criteria for response or relapse and those who were lost to follow-up without a documented response or relapse, as well as those who did not meet response or relapse criteria at their last assessment. The number of sessions attended by patients was also compared. Nested ANOVA was conducted on the primary outcomes to explore the nesting effect of different therapists. We also used stepwise multivariate regression model to estimate which factors affected the PANSS Total score and the Positive score.

3. Results

3.1. Participant flow and characteristics

Fig. 1 shows the CONSORT diagram. After exclusion of patients who did not meet the inclusion criteria, eighty patients were randomly assigned to CBT + TAU (treatment group) or TAU group. During the study, a total of 13 patients withdrew. Patients assigned to CBT received a mean of 7.4 sessions (Range 4–10; SD = 2.1). 31 (77.5%) of the 40 patients had at least six sessions, suggesting good adherence to treatment group. The 62-week follow-up was completed by 35 participants (87.5%) in the treatment group and 29 participants (72.5%) in the TAU group. There was no significant difference between two groups in terms of the proportion or the demographic and clinical characteristics of patients who failed to complete the assessment at any time point (See Supplemental Table 1). There was no significant difference in terms of the demographic and clinical characteristics of patients between completers and non-completers at week 62 (See Supplemental Tables 2–4).

The mean age was 26.35 (SD = 7.41) for treatment group, 28.6 (SD = 5.86) for TAU, and approximately 35% were woman in treatment group and 50% in the control group. There were no statistically significant differences at baseline between the two groups in demographic characteristics (age, gender, education background, marital and occupation status) or in clinical characteristics (duration of illness, PANSS, SAI, PSYRATS and PSP scores) (Table 1). The treatment group took a 391–389 mg equivalent of chlorpromazine, and the TAU group took a 356–339 mg equivalent of chlorpromazine from baseline to 62 weeks. There were also no significant difference in antipsychotic medication use at baseline to week 62 in chlorpromazine equivalents (Table 2). Overall, participants were clinically stable at baseline – while they had scores of above 4 on P1 or P3 on the PANSS (as stated in the inclusion criteria), no participants scored above 10 when totaling the sub-set of items measuring thought-disorder (conceptual disorganisation (P2), hallucinatory behaviour (P3), grandiosity (P5) and unusual thought content (G9)) and none of these items scored 6 or above.

Table 1
Comparison of baseline demographic and clinical characteristics between CBT + TAU and TAU group.

Variables	CBT + TAU group (n = 40)	TAU group (n = 40)	$t/\chi^2/z$	P
Age, years: mean (s.d.)	26.35 (7.41)	28.60 (5.71)	$t = -1.485$	0.132
Gender			$\chi^2 = 1.841$	0.175
Male	26	20		
Female	14	20		
Education, years: mean (s.d.)	13.30 (2.95)	13.00 (2.29)	$t = 0.496$	0.613
Marital status (n)			$\chi^2 = 2.581$	0.108
Married	28	21		
Single	12	19		
Employment (n)			$\chi^2 = 0.487$	0.485
Yes	16	13		
No	24	27		
PANSS total: mean (s.d.)	68.48 (15.67)	69.08 (15.91)	$t = -0.170$	0.866
Positive Scale: mean (s.d.)	17.88 (5.40)	18.68 (5.76)	$t = -0.641$	0.523
Negative Scale[a]: media (range)	15 (7–24)	15 (7–24)	$z = 0.275$	0.783
General Scale[a]: media (range)	33.5 (20–52)	36.5 (19–55)	$z = 0.419$	0.675
PSYRATS[a]: media (range)	27.5 (10–55)	32.5 (11–57)	$z = -0.905$	0.365
SAI: mean (s.d.)	7.10 (3.55)	6.80 (3.63)	$t = 0.374$	0.709
PSP: mean (s.d.)	52.88 (13.72)	53.18 (14.83)	$t = 0.094$	0.925

CBT, Cognitive-behavioural therapy; TAU, Treatment as usual; PANSS, Positive and Negative Syndrome Scale; SAI, Schedule for Assessing Insight; PSYRATS, Psychotic Symptoms Rating Scale; PSP, Personal and Social Performance.
[a] For skewed distributions, Mann–Whitney U tests were used.

3.2. Outcomes

3.2.1. Primary outcomes

By the end of the trial, four participants (10%, 4/40) in the CBT group had relapsed compared to thirteen participants (32.5%, 13/40) in the TAU group. Similarly, three participants (7.5%, 3/40) in the CBT group had been admitted to hospital compared to eight participants (20%, 8/40) in the TAU group, though this was not statistically significant ($\chi2 = 3.529$, $P = 0.06$). To overcome overdispersion caused by zero-inflation of the count data, zero-inflated Poisson models were used to compare counts of hospitalization and relapse between groups. Between the two group there was no significant difference in hospitalization ($Z = -1.397$, $P = 0.162$), but there was significant difference in relapse ($Z = -2.019$, $P = 0.044$).

Using the criterion of a 25% or greater reduction on the PANSS total score, 47.5% (19/40) of those in the CBT group experienced a clinically significant improvement compared with only 25% (10/40) of those in TAU alone group. This difference was statistically significant ($\chi2 = 4.381$, $P = 0.036$) and indicates that the CBT intervention had a more clinically meaningful effect on overall symptoms. The number needed to treat for improvement in overall symptoms was 4, which means that for every four patients treated with CBT there was one additional patient who demonstrated a clinically significant improvement over TAU. Similarly, using the criterion of a 25% or greater reduction in PANSS positive score, 85% (34/40) of those in the CBT group experienced a significant improvement compared with 65% (26/40) of those in TAU alone group. This difference was statistically significant ($\chi2 = 14.267$, $P = 0.039$). The number needed to treat for improvement in positive symptoms was 5. The difference between the survival curves was significant for both response in positive symptoms (log rank = 5.413, $P = 0.020$) and relapse (log rank = 6.073, $P = 0.014$) (see Figs. 2 and 3).

Table 3 shows the main effect of time, group and time × group interaction on each symptom outcome using ITT analysis. A main effect of time was found for PANSS-Total, PANSS–Positive, PANSS-Negative and PANSS-General subscales, as well as PSYRATS, indicating a significant decrease over time across groups for all symptom assessments.

However, for total symptoms, there was a significant time × group interaction, indicating that the CBT group showed greater decreases in total symptoms than the TAU group at follow-up (At baseline, $F(1,78) = 0.029$, $P = 0.866$; At 10 weeks, $F(1,78) = 3.136$, $P = 0.080$; At 36 weeks, $F(1,78) = 5.987$, $P = 0.017$; At 62 weeks, $F(1,78) = 14.135$, $P < 0.001$). Similarly, for general symptoms, there was a significant time × group interaction, indicating that the CBT group showed greater decreases in general symptoms over time (At baseline, $F(1,78) = 0.066$, $P = 0.798$; At 10 weeks, $F(1,78) = 2.319$, $P = 0.132$; At 36 weeks, $F(1,78) = 6.146$, $P = 0.015$; At 62 weeks, $F(1,78) = 13.890$, $P = 0.000$) (See Supplemental Table 5).

For positive symptoms, there was also a main effect of group but no significant time × group interaction (At baseline, $F(1,78) = 0.411$, $P = 0.523$; At 10 weeks, $F(1,78) = 2.329$, $P = 0.131$; At 36 weeks, $F(1,78) = 1.809$, $P = 0.182$; At 62 weeks, $F(1,78) = 11.866$, $P = 0.001$). Similarly, for PSYRATS, there was a main effect of group, but there was no significant time × group interaction, indicating that the CBT group had significantly lower scores than the TAU group on delusions and auditory hallucinations (At baseline, $F(1,78) = 0.791$, $P = 0.376$; At 10 weeks, $F(1,78) = 10.270$, $P = 0.002$; At 36 weeks, $F(1,78) = 9.022$, $P = 0.004$; At 62 weeks, $F(1,78) = 14.234$, $P < 0.001$). For negative symptoms, there was no significant time × group interaction or main effect of group, indicating that the two conditions resulted in significant reductions of negative symptoms, but with no significant difference across conditions (At baseline, $F(1,78) = 0.044$, $P = 0.834$; At 10

Table 2
Changes in prescribed antipsychotic drugs.

Assessment	CBT + TAU group (n = 40)	TAU group (n = 40)	t	P
Chlorpromazine equivalents, mg				
Baseline	391.20(199.68)	356.00(201.06)	$t = 0.776$	0.440
10 weeks	383.70(185.19)	354.68(205.25)	$t = 0.656$	0.514
36 weeks	389.33(185.74)	349.42(201.32)	$t = 0.910$	0.365
62 weeks	389.33(185.74)	339.95(199.54)	$t = 1.125$	0.264

CBT, Cognitive-behavioural therapy; TAU, Treatment as usual.

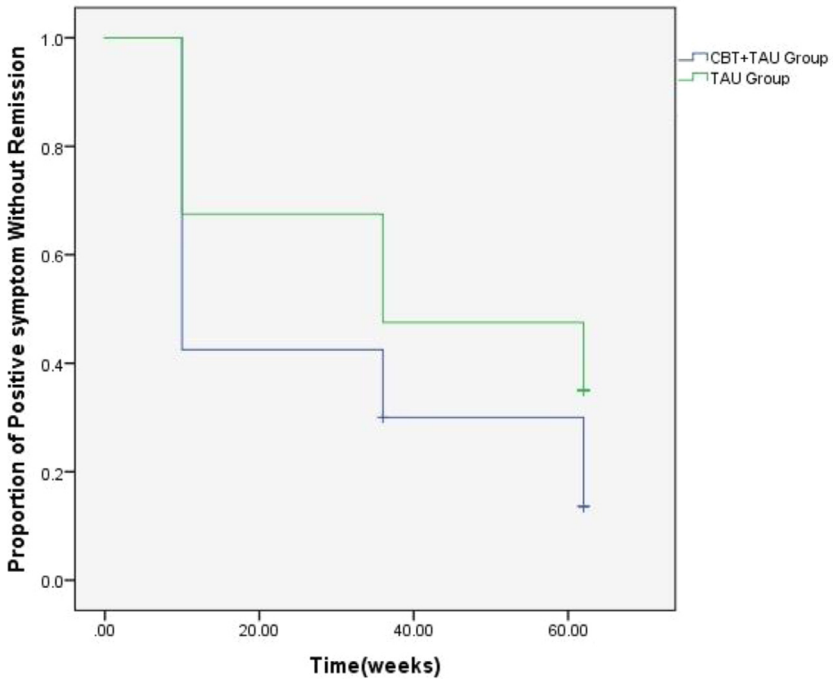

Fig. 2. . Kaplan-Meier estimates of times to response; CBT, Cognitive-behavioural therapy; TAU, Treatment as usual.

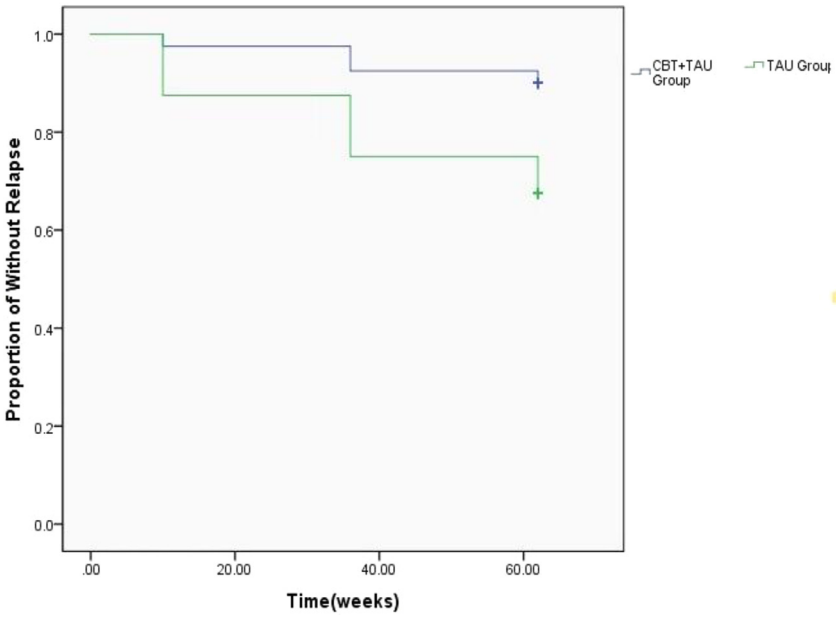

Fig. 3. . Kaplan-Meier estimates of times to relapse; CBT, Cognitive-behavioural therapy; TAU, Treatment as usual.

weeks, F(1,78) = 1.064, $P = 0.306$; At 36 weeks, F(1,78) = 1.732, $P = 0.193$; At 62 weeks, F(1,78) = 4.443, $P = 0.038$) (See Supplemental Table 5).

Our nested ANOVA analysis indicated that there was a significant difference between therapists regarding improvement in PANSS Positive scale and PSYRATS (F = 2.902, $P = 0.040$; F = 4.735, $P = 0.004$); there were no significant differences for PANSS Total, Negative Scale, General Scale, SAI, PSP (F = 2.603, $P = 0.058$; F = 0.511, $P = 0.676$; F = 2.244, $P = 0.090$; F = 0.733, $P = 0.536$; F = 0.853, $P = 0.470$). Sub analyses indicated that the difference was driven by therapist 2 and 4 (See Supplemental Table 6).

The stepwise multivariate regression analyses indicated that lower baseline negative PANSS score predicted lower PANSS total score at week 62 ($P < 0.001$). Similarly, lower baseline PANSS total score ($P < 0.001$) and more treatment sessions ($P = 0.014$) predicted lower PANSS positive score at week 62 (See Supplemental Table 7 and 8).

3.2.2. Secondary outcomes

Analyses of the SAI total score and PSP both revealed main effects of time, suggesting an increase in insight and functioning over time for both groups. However, there was a main effect of time x group interaction for PSP scores indicating that the CBT group had significantly higher levels of functioning compared with the TAU group at follow up (At baseline, $F(1,78) = 0.001$, $P = 0.980$; At 10 weeks, $F(1,78) = 5.329$, $P = 0.024$; At 36 weeks, $F(1,78) = 4.523$, $P = 0.037$; At 62 weeks, $F(1,78) = 6.616$, $P = 0.012$). In contrast, there was no

Table 3
Repeated-measures analysis of variance (ANOVA) in clinical symptoms, insight and social functioning by group at the four time points.

Outcomes, group	Baseline (n = 40)	10 weeks (n = 40)	36 weeks (n = 40)	62 weeks (n = 40)	Value (ITT) Time	Group	time × group
PANSS total					F = 102.757 P = 0.000	F = 5.475 P = 0.022	F = 3.376 P = 0.042
CBT + TAU	68.48(15.67)	51.65(11.22)	44.88(8.06)	43.20(7.89)			
TAU	69.07(16.33)	55.05(9.56)	49.60(10.47)	52.00(13.92)			
Positive scale					F = 102.122 P = 0.000	F = 4.603 P = 0.035	F = 1.342 P = 0.265
CBT + TAU	17.87(5.40)	11.92(4.10)	9.97(2.48)	9.42 (2.62)			
TAU	18.68(5.76)	13.17(3.17)	10.85(3.29)	12.03(3.99)			
Negative scale[a]					F = 17.513[a] P = 0.000[a]	F = 1.753[a] P = 0.189[a]	F = 1.443[a] P = 0.237[a]
CBT + TAU	15 (7–24)	13(7–20)	11 (7–19)	11 (1–19)			
TAU	15(7–24)	14(7–20)	13(7–22)	11.5(7–26)			
General scale[a]					F = 82.534[a] P = 0.000[a]	F = 5.143[a] P = 0.026[a]	F = 3.884 [a] P = 0.027[a]
CBT + TAU	33.5(20–52)	27(16–39)	23 (16–34)	23(16–30)			
TAU	36.5(19–55)	27.5(18–42)	24.5(16–43)	26 (17–46)			
PSYRATS[a]					F = 97.319[a] P = 0.000[a]	F = 12.215[a] P = 0.001[a]	F = 1.945[a] P = 0.024[a]
CBT + TAU	27.5(10–56)	9.5(1–40)	3(1–23)	2(1–26)			
TAU	32.5(11–57)	18.5(4–42)	7(1–47)	7(1–50)			
SAI					F = 37.760 P = 0.000	F = 2.428 P = 0.123	F = 0.814 P = 0.458
CBT + TAU	7.10(3.55)	10.00(3.15)	11.08(3.27)	11.02(3.03)			
TAU	6.80(3.63)	9.10(3.12)	9.98(3.48)	9.58(3.85)			
PSP					F = 78.444 P = 0.000	F = 4.475 P = 0.055	F = 3.119 P = 0.039
CBT + TAU	52.88(13.72)	66.42(11.86)	74.75(10.14)	75.73(11.88)			
TAU	52.79(14.83)	59.00(16.42)	68.74(14.62)	67.85(15.18)			

CBT, Cognitive-behavioural therapy; TAU, Treatment as usual; PANSS, Positive and Negative Syndrome Scale; PSYRATS, Psychotic Symptoms Rating Scale; PSP, Personal and Social Performance.

[a] For skewed distributions, the original data were turned into reciprocal firstly, then performed repeated-measures analysis of variance.

main effect of group or significant time × group interaction for SAI total score (At baseline, $F(1,78) = 0.140$, $P = 0.709$; At 10 weeks, $F(1,78) = 1.650$, $P = 0.203$; At 36 weeks, $F(1,78) = 2.126$, $P = 0.149$; At 62 weeks, $F(1,78) = 3.501$, $P = 0.065$) (See Table 3 and Supplemental Table 5).

The CBT group had significantly better employment outcomes than TAU Group ($\chi 2 = 4.053$, $P = 0.044$); 24 participants in the CBT group had a current employment position at the end of 62 weeks compared to 15 participants in the TAU group.

4. Discussion

This study demonstrates that a brief CBT targeting relapse prevention and positive symptom was effective in first episode schizophrenia patients. Specifically, compared with treatment-as-usual, it was associated with significantly greater reductions in relapse, as well as significantly greater improvements in positive, general and overall psychotic symptoms and social functioning (including employment status). This study also demonstrates that this adapted brief CBT model is feasible and acceptable in a Chinese FES population, as indicated by a low drop-out rate.

Previous CBT interventions focusing on general psychotic symptoms have shown inconsistent results for reducing positive symptoms in first episode psychosis (Haddock et al., 1999b; Jackson et al., 2008; Lewis et al., 2002). The present study suggests that the positive symptom management aspect of the intervention in our study may have played an important role in overall symptom reduction.

A previous systematic review concluded that CBT intervention were not especially effective in reducing rates of relapse or hospital admission in FEP (Morrison, 2009). However, our study reports significantly greater reductions in relapse for participants who received CBT compared to TAU alone, and a trend for reduced hospitalization. There are number of explanations for this. First, the targeted relapse prevention focus of our CBT intervention may have had a direct, unique and specific effect on reducing relapse risk. Second, the CBT intervention was associated with greater positive symptom compared with those in TAU group, which may be critical in preventing relapse in FES (Lavretsky, 2008; Patel et al., 2014). Third, the relapse and hospitalization rate in this study was low compared to previous studies with inpatient sample population. For instance, Jolley et al. (2003) report a hospitalization rate of 25% for the cognitive therapy group and 22.2% in TAU group in early psychosis patients, and Tarrier et al. (2004) found the relapse rates/hospital readmission in CBT, supportive counselling, TAU group were 54.6%/33%, 52.1%/29% and 51.1%/36%, respectively. However, the present study targeted an outpatient sample with less severe symptoms. Future studies should evaluate the effectiveness of this CBT intervention for hospitalized FES patients with more severe psychotic symptoms.

Part of patients' acceptance of their illness and self-knowledge is recognising the importance of treatment, which is associated with subsequent improved adherence to medication (Bedford and David, 2014; Wang et al., 2003) and reduced relapse rates and hospital readmissions (Kemp et al., 1996). A number of previous studies have demonstrated that CBT can improve insight in first episode psychosis patients (Jackson et al., 1998; Wang et al., 2003), potentially via psychoeducation or behavioural experiments (Rathod et al., 2005). Interestingly, in the present study we found that both groups had high SAI scores at 1 year with significant improvements in insight over time. Although patients in the CBT group showed higher insight scores than TAU, the failure to find a significant group difference in this study may in part be due to patients in the TAU group experiencing regular contact with their psychiatrist and clinicians assessing them for research, who may have offered informal supportive consulting.

Impairment in social and occupational functioning is common following first episode psychosis (Penn and Mueser, 1996). Our study reports that the CBT group had significant improvements in their general psychosocial functioning, which is in line with previous studies (Jackson et al., 1998; Penn et al., 2005; Power et al., 2003). This may have been driven by standard CBT intervention techniques, such as problem-solving skills, stress management and behavior activation, or the targeted focused on reducing relapse rates. We also found that CBT group had better occupational functioning (reflected in their current employment status) than TAU. Previous evidence indicates that CBT is a particularly promising intervention to improve work-related beliefs and

behaviors, resulting in enhanced employment outcome (Kukla et al., 2016; Lysaker et al., 2009). Importantly, a recent study conducted by Kukla et al. (2018), found that participants with schizophrenia spectrum disorders who were allocated to receive CBT with cognitive remediation (CR) had significantly more positive improvements in global work performance and work quality compared with being allocated to receive the vocational support group and CBT alone. The authors suggested that improving memory and capacity for learning and problem solving through CR intervention could amplify the effects of CBT for better employment outcomes (Kukla et al., 2018). It would be worthwhile for future research to examine CBT with CR in FES populations.

It is worth noting that definitions and measurements of relapse, when relying on hospitalization, may vary between countries. In many developed countries, relapse can be treated at outpatient and community clinic services without being admitted to hospital due to the establishment of community mental health teams, but that is not true for China. Although China has established a three-tier network (from town to district and city levels) based on community health services for the treatment and prevention of psychosis, most of the community health service remain limited, suffering from a severe lack of mental health professional workforce, service capabilities and inadequate regulatory resources (Tse et al., 2013). There is also a significant urban-rural disparity in community health service development (Liu et al., 2011). The key responsibility for community health services is to reduce the possibility of criminal offending among people with severe psychosis (Xiang et al., 2012). Furthermore, specialist psychiatrists are concentrated in large general hospitals or specialized psychiatry hospitals and practitioners at community health clinics are not similarly equipped with the sufficient and experienced qualifications. Therefore, we would have expected a higher rate of hospitalisation for relapse in China than other countries and it is surprising that we found lower rates.

In addition, while few studies have investigated the association between stigma and psychiatric re-hospitalization, some studies - for instance, Alex (2012) – have found that stigma about mental disorder within a family can lead to higher rates of re-hospitalization for relatives with psychosis; perhaps due to neglecting the need for treatment leading to worsened symptoms. In Chinese culture, the role of Confucianism is significant and impacts upon understanding of mental health disorders and stigma. The collectivistic tradition encourages people to maintain social and familial harmony, and the notion of “saving face” is of crucial importance to social identity and hierarchy (Xi et al., 2017). Therefore, people suffering from mental health disorders are equated with extreme shame for the whole family. Although numerous studies have investigated the stigma and self-stigma among schizophrenia patients in Chinese populations (Lv et al., 2013; Phillips et al., 2002), none have examined the influence of stigma and re-hospitalization. Again, while literature from other countries may have indicated increased hospitalization rates due to increased stigma in China, we found unusually low rates; this may reflect a different relationship with stigma than expected (stigma may delay or discourage seeking necessary hospitalisation) or may be reflective of the specific hospital or region.

The present study has several limitations. Firstly, while we assessed patients at numerous follow ups over one year, this follow up period is still too brief to explore the full long-term effects of CBT on symptoms, functioning, insight and relapse in FES patients. Secondly, the sample did not include patients with severe symptoms requiring hospitalization, impacting on generalizability. Future study should examine whether a brief CBT intervention has similar outcomes for FES inpatients or patients with more severe symptoms. Thirdly, we did not use a standardized measure of treatment fidelity such as the Cognitive Therapy Scale to check treatment fidelity. This is because such a scale has not been developed in China; we would strongly encourage future research to pursue this to help ensure high quality of clinical trials. Fourthly, there was variability in outcomes related to therapist assignment, with significant differences between therapist 2 and therapist 4 on improvement measured by both PANSS Positive sub-scale and PSYRATS. It is unclear whether this may have been due to non-random assignment of therapists. Finally, this study did not use active treatment as a control group, meaning that non-specific therapeutic factors may have driven group differences – for example, the format of more frequent regular sessions and subsequent increased focus and attention on the participant may drive the effect in the treatment group. Therefore, we cannot conclusively say which element of the brief CBT intervention drives it efficacy or whether a non-specific intervention would find similar effects.

In summary, this is the first RCT study indicating effectiveness of a brief CBT intervention focused on relapse prevention in patients with first-episode schizophrenia. This positive finding suggests that more research is warranted exploring the effects of CBT for first episode psychosis, specifically targeting relapse prevention and positive symptom.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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