ORIGINAL ARTICLE

Effect of Antipsychotic Medication Alone vs Combined With Psychosocial Intervention on Outcomes of Early-Stage Schizophrenia

A Randomized, 1-Year Study

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Context: Antipsychotic drugs are limited in their ability to improve the overall outcome of schizophrenia. Adding psychosocial treatment may produce greater improvement in functional outcome than does medication treatment alone.

Objective: To evaluate the effectiveness of antipsychotic medication alone vs combined with psychosocial intervention on outcomes of early-stage schizophrenia.

Design: Randomized controlled trial.

Setting: Ten clinical sites in China.

Participants: Clinical sample of 1268 patients with early-stage schizophrenia treated from January 1, 2005, through October 31, 2007.

Intervention: Patients were randomly assigned to receive antipsychotic medication treatment only or antipsychotic medication plus 12 months of psychosocial intervention consisting of psychoeducation, family intervention, skills training, and cognitive behavior therapy administered during 48 group sessions.

Main Outcome Measures: The rate of treatment discontinuation or change due to any cause, relapse or remission, and assessments of insight, treatment adherence, quality of life, and social functioning.

Results: The rates of treatment discontinuation or change due to any cause were 32.8% in the combined treatment group and 46.8% in the medication-alone group. Comparisons with medication treatment alone showed lower risk of any-cause discontinuation with combined treatment (hazard ratio, 0.62; 95% confidence interval, 0.52-0.74; $P<.001$) and lower risk of relapse with combined treatment (0.57; 0.44-0.74; $P<.001$). The combined treatment group exhibited greater improvement in insight ($P<.001$), social functioning ($P=.002$), activities of daily living ($P<.001$), and 4 domains of quality of life as measured by the Medical Outcomes Study 36-Item Short Form Health Survey (all $P\leq.02$). Furthermore, a significantly higher proportion of patients receiving combined treatment obtained employment or accessed education ($P=.001$).

Conclusion: Compared with those receiving medication only, patients with early-stage schizophrenia receiving medication and psychosocial intervention have a lower rate of treatment discontinuation or change, a lower risk of relapse, and improved insight, quality of life, and social functioning.

Trial Registration: clinicaltrials.gov Identifier: NCT00654576

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ANTIPSYCHOTIC DRUGS HAVE been shown to be effective against psychotic symptoms, and they are now the mainstay of therapy for patients with schizophrenia.[1,2] However, long-term therapy with antipsychotics is associated with a range of adverse effects, poor adherence, and high rates of medication discontinuation.[2-4] Most patients, even those with a good response to medication, continue to experience disabling residual symptoms, impaired social and occupational functioning, and a high risk of relapse. Certain psychosocial treatments have been shown to have beneficial effects on clinical and functional outcomes.[5-9] For instance, family intervention reduces relapse rate,[5] cognitive behavior therapy reduces positive symptoms,[5,8] and social skills training improves social competence.[7] The combination of pharmacotherapy and psychosocial intervention has been recommended for treatment of schizophrenia by practice guidelines for psychiatrists.[10] Psycho-

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social interventions can be best implemented when acute symptoms have been reduced and the patient can be successfully engaged in treatment. The goals of intervention are to reduce stress on the patient, provide support to minimize the likelihood of relapse, enhance the patient's adaptation to life in the community, and facilitate continued reduction in symptoms and consolidation of remission.[10] However, the effectiveness of psychosocial intervention approaches has been considered separately. Each intervention has been directed toward one of the components of the problem: the patient's symptoms, relapse, or social skills. Few comprehensive psychosocial intervention packages have been developed that can address several problems simultaneously in schizophrenia.

Early illness course is an important predictive factor for the long-term outcome; intervention during this critical period is considered important.[11] As with the published literature on chronic schizophrenia treatment, studies of first-episode and early schizophrenia samples have shown that they benefit from medication management integrated with a variety of psychosocial treatments. For example, the OPUS trial used an intensive early-intervention approach combining assertive community treatment, family psychoeducation, and social skills training, with positive effects on hospitalization rates, living independence, symptom severity, and family burden.[12,13] Integrated treatment with medication, skills training, and cognitive behavior therapy is another approach that has been used, with positive effects on symptom severity.[14] Finally, medication has also been integrated with cognitive behavior therapy, family support, and vocational services, with positive effects on hospital readmission, functioning, and medication adherence.[15,16]

In this article, we report on the Antipsychotic Combination With Psychosocial Intervention on the Outcome of Schizophrenia Study (funded by the Ministry of Science and Technology of China), a 1-year randomized clinical trial that tested the effect of medication combined with a group psychosocial intervention vs medication treatment alone on outcomes of patients with early-stage schizophrenia.[17] The outcomes measured included the rate of treatment discontinuation or change due to any cause, relapse or remission, and assessments of insight, treatment adherence, quality of life, and social functioning. We hypothesized that combined medication and comprehensive psychosocial treatment would result in lower rates of treatment discontinuation or relapse than would medication treatment alone, which would reflect variations in efficacy, insight and adherence, quality of life, social outcome, and adverse effects.

METHODS

PARTICIPANTS

The study was conducted between January 1, 2005, and October 31, 2007, at 10 clinical sites in China (6 university clinics and 4 province mental health agencies). All patients were enrolled from outpatient psychiatric clinics and were under maintenance treatment. Eligible patients were those 16 to 50 years of age who met the following enrollment criteria: (1) *DSM-IV* diagnosis of schizophrenia or schizophreniform disorder within the past 5 years, as determined by the Structured Clinical Interview for *DSM-IV* Axis I Disorders–Clinician Version[18] administered by study investigators or trained staff; (2) living with family members who could be involved in the patient's care; (3) Positive and Negative Syndrome Scale (PANSS)[19] total score of 60 or less; (4) receiving maintenance treatment with one of the following 7 oral antipsychotics: chlorpromazine hydrochloride, sulpiride, clozapine, risperidone, olanzapine, quetiapine fumarate, or aripiprazole. We selected these 7 antipsychotics because more than 90% of schizophrenic patients in China were prescribed one of these antipsychotics.[20] Patients were excluded if they were (1) prescribed 2 or more antipsychotics or long-acting injectable antipsychotics, (2) participating in other therapy programs, (3) pregnant or breastfeeding, or (4) diagnosed as having a serious and unstable medical condition. This study was approved by the institutional review board at each site, and written informed consent was obtained from the patients or their legal guardians.

PROCEDURE

After baseline assessment, participants were randomly assigned to receive combined medication and psychosocial treatment or medication treatment alone and were monitored for up to 12 months or until medication treatment was discontinued for any reason. Group assignment was based on a 1:1 randomization scheme balanced by sites and medication prescribed. All medication visits and interventions took place in the outpatient psychiatric clinics in these participating institutes. Members of both study groups came to medication management visits once a month, and the therapy was given on the same day for the combined treatment group. The family members had to bring the patient to each appointment, regardless of treatment group. All patients and their family members from both study groups came to the clinic once a month and received the same compensation for participating in the study. No transportation, outreach, or other logistic supports were provided by this study. In both groups, patients and family members could ask medication- or treatment-related questions of the treating clinicians during their 30-minute visit as standard of outpatient care for medication management. To better keep the assessors and clinicians blinded, the psychotherapy rooms, clinicians' offices, and assessors' offices were isolated from each other; patients and family members were reminded at enrollment and follow-up visits not to discuss treatment assignment with their clinicians and assessors; and investigators and staff were restricted in the discussion of patients within research teams. Further detail about the study rationale, design, and methods have been described previously.[17]

INTERVENTIONS

Pharmacotherapy

Because all patients were receiving maintenance treatment, we encouraged clinicians to try to keep patients on the same medication regimen for 3 to 6 months to gauge treatment efficacy and minimize early discontinuation. However, medications could be changed at any time during the course of the study if the change was clinically warranted. If a patient's medication was stopped or switched, patients were classified as discontinued and were terminated from the study. No further assessments were required for these patients. Mood stabilizers, benzodiazepines, antidepressants, and anticholinergic medications were permitted, and daily doses of all medications were recorded throughout the study.

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Table 1. Content of Monthly Psychosocial Treatment Sessions

Month	Psychoeducation Topics	Family Intervention Topics	Skills Training Topics	Cognitive Behavior Therapy Topics
1	Introduction into program; discussion of goals and questions	Introduction into program; discussion of goals and questions	Medication management 1: identifying benefits of antipsychotic medication	Developing therapeutic alliance
2	What is schizophrenia?	Role of family in schizophrenia	Medication management 2: self-administration and evaluation of medication	Using the "ABC Model" to find connections between *a*ctivating events, *b*eliefs, and *c*onsequences
3	Causal and triggering factors	Relatives sharing experiences of caring for patients	Medication management 3: adverse effects of antipsychotic medication	Intervening with auditory hallucinations (voices)
4	Description of various symptoms	Coping strategies: identifying, describing, clarifying, and teaching coping strategies used by families	Symptom management 1: identifying warning signs of relapse	Intervening with auditory hallucinations (voices)
5	Patients' concepts of illness and vulnerability-stress-coping model	Coping strategies: identifying, describing, clarifying, and teaching coping strategies used by families	Symptom management 2: developing relapse prevention plan	Intervening with delusions
6	Course and outcome	Helping families with problem solving	Verbal and nonverbal communication	Intervening with delusions
7	Treatment recommendations concerning pharmacotherapy	Helping families with problem solving.	Verbal and nonverbal communication	Intervening with anxiety, depression, and self-esteem issues
8	Risks associated with treatment withdrawal	Family communication	Learning and practicing problem-solving skills	Intervening with anxiety, depression, and self-esteem issues
9	Early detection of relapse	Family communication	Learning and practicing problem-solving skills	Relapse prevention
10	Pregnancy and genetic counseling	Behavior management	Job-finding skills	Relapse prevention
11	Discussion of open questions	Behavior management	Independent living skills	Enhancing medication adherence
12	Final session: review of content	Final session: review of content	Independent living skills	Enhancing medication adherence

Psychosocial Intervention

Patients assigned to the combined treatment group received medication treatment and were enrolled in a psychosocial intervention program. The psychosocial intervention strictly followed a detailed treatment manual designed by the principal investigators (Drs X. Guo, Liu, and Zhao) and included 4 evidence-based practices: psychoeducation, family intervention, skills training, and cognitive behavior therapy.[21] Participants receiving psychosocial intervention were seen 12 times (once per month for 12 months), receiving each of the 4 group treatments on the same day, for a total of 48 one-hour sessions (see **Table 1** for topics covered). A lunch break and 2 half-hour breaks were provided to maintain engagement and attention. We designed this comprehensive psychosocial intervention to be delivered on the same day once a month mainly owing to the care structure in China, the potential time and cost burden to patients and their family members, and the feasibility of adoption by other care settings. In China, most patients with schizophrenia live with their family members because of limited social welfare for severely mentally ill patients. Many of these family members also work full time, so it is not convenient for them to take time off every week and bring the patients for therapy. In addition, all our psychosocial interventions were group based, so having many patients and their family members come in once a week at the same time was not feasible or practical. Weekly intervention visits also would have increased the costs of transportation and therapist time, making the overall cost of the psychosocial intervention higher. Finally, psychosocial interventions have become more popular in recent decades in China, but the number of well-trained therapists remains limited in many Chinese psychiatric settings. More frequent therapy sessions could be not only difficult for patients and family members but also hard for many psychiatric settings to adopt.

Psychoeducation included teaching patients and caregivers about the symptoms, treatment, and course of mental illness and afforded patients and family members the opportunity to ask questions about psychiatric disorders and treatment options. This group provided a forum in which to discuss concerns and obtain support from the group to reduce the stigma of mental illness. The purpose of psychoeducation was to increase patients' and caregivers' knowledge and understanding of the illness and treatment.[22-24]

Family intervention included developing collaboration with the family, socializing about non–illness-related topics, monthly updates on each family's situation, enhancing family communication, teaching patients and their families to cope with stressful situations and the illness, and teaching patients and their families to detect signs of relapse and intervene in crises.[22,25,26]

Skills training included modules on medication management and symptom self-management, dealing with stigma, social problem solving, and independent living skills. The training included teaching complex interpersonal skills by breaking down the targeted behaviors into component steps and systematically using modeling, behavioral rehearsal, positive and corrective feedback, and in vivo practice to shape the acquisition and generalization of skills.[7,27-29]

Cognitive behavior therapy involved treatment of auditory hallucinations, delusions, and associated symptoms and problems (ie, anxiety, depression, and self-esteem); prevention of relapse; and enhancement of medication adherence. Treatment included an assessment and engagement phase, education, and building a therapeutic alliance; functional analysis of

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key symptoms, leading to formulation of a problem list; development of a normalizing rationale for the patients' psychotic experiences; and exploration and enhancement of coping strategies. Concomitant affective symptoms were addressed by means of relaxation training.[30,31]

Therapists who had at least 2 years of clinical experience after earning an MD or PhD or at least 5 years of experience after earning a masters degree in clinical psychology delivered the psychosocial intervention. They attended training workshops until they had mastered all treatment procedures. Treatment fidelity was maintained by having the therapists' supervisors assess adherence to the treatment manual after each monthly session by reviewing videotapes.

OUTCOME ASSESSMENTS

All subjects were assessed monthly by the study psychiatrists and every 2 weeks by a research assistant who had instructions to contact the psychiatrist if medication discontinuation, relapse, or other problems were suspected. The psychiatrists assessed patients mainly for medication management purposes, evaluating for clinical response to medications, medication adherence, and major adverse effects. The research assistants assessed patients, patients' caregivers, and other sources every 2 weeks by telephone for any hospitalizations, relapses, or other causes of treatment discontinuation. The research assistants also administered the symptom and functioning rating scales at scheduled intervals. The primary measure was rate of treatment discontinuation or change and time to treatment discontinuation. Once a patient discontinued the study, no further assessments were completed. Our criteria for treatment discontinuation or change were somewhat broader than those of the Clinical Antipsychotic Trials of Intervention Effectiveness study[2] and included (1) clinical relapse/hospital admission; (2) loss to follow-up or patient's refusal; (3) nonadherence, defined as taking less than 70% of prescribed medications, detected by either the treating psychiatrist or research assistants during follow-up assessments; (4) changing or stopping of the initial antipsychotic medication by physician or patient request; and (5) intolerability, defined as severe adverse effects that caused the treating psychiatrists to stop the medication.

Clinical relapse was defined by any one of the following[32]: (1) psychiatric hospitalization; (2) an increase in the level of psychiatric care (eg, from clinic visits to day treatment) and a 25% or more increase in the PANSS total score (or 10 points if the initial score was ≤40); (3) a Clinical Global Impressions Scale score of "much worse" or "very much worse"[33(pp218-222)]; (4) deliberate self-injury; (5) emergence of clinically significant suicidal or homicidal ideation; or (6) violent behavior resulting in significant injury to another person or significant property damage.

Secondary outcomes further assessed treatment effectiveness by measuring symptom severity (PANSS), insight (Insight and Treatment Attitudes Questionnaire [ITAQ]),[34] treatment adherence (appointment adherence), quality of life (Medical Outcomes Study 36-Item Short Form Health Survey [SF-36]),[35,36] and social functioning on the Global Assessment Scale (GAS)[37] and the Activities of Daily Living Scale (ADL).[38,39] The SF-36 consists of 8 domains that assess bodily pain, general health, general mental health, physical functioning, role-emotional, role-physical, social functioning, and vitality. The GAS is a single-item rating scale for evaluation of overall patient functioning.[37] The 14-item independent ADL assesses a person's ability to perform basic (eg, dressing, walking, and bathing) and instrumental (eg, using a telephone, doing laundry, and handling finances) activities of daily living.[38,39] This scale has been widely used and has demonstrated validity in studies of medically ill and dementia populations in China.[40,41] The rate of obtained work or education during the 12 months was also used to assess role functioning and community integration. The physical examination and the effect of antipsychotic treatment on weight gain were recorded regularly. The Treatment Emergent Symptom Scale[33(pp341-350)] was used for monitoring adverse effects.

All interviewers trained and received reassessments of interrater reliability on the basis of videotaped demonstration interviews. Agreement among the raters was high for the PANSS, ITAQ, GAS, and ADL (Pearson correlation coefficient, 0.78-0.86) at baseline and every 6 months.

STATISTICAL ANALYSIS

Analyses were performed according to the intention-to-treat principle. Randomized patients who had at least 1 assessment during treatment made up the intention-to-treat population. The sample sizes were selected to make possible the detection of a 15% difference in discontinuation rates after 1 year with 85% power and a 2-tailed α level of significance of .05.

Baseline characteristics were compared between the 2 groups by analysis of variance, Pearson χ^2 test, or Fisher exact test, as appropriate. We used Kaplan-Meier survival curves to estimate the time to discontinuation of treatment in the sample. Factors associated with treatment discontinuation were determined by multivariate analysis using a Cox proportional hazards model with stepwise reduction and a log-rank test with control for site.[42] Data were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Time course and treatment differences for change in the PANSS, ITAQ, SF-36 domain scores, GAS, and ADL were analyzed by means of a mixed-effects model for repeated-measures analyses with effects of treatment, time, and treatment × time interaction with unrestricted covariance of baseline scores.[43] Time was classified into months (baseline and 3, 6, 9, and 12 months). Other categorical outcomes (including data regarding adverse events) were compared with the use of Pearson χ^2 test or Fisher exact test. All statistical tests were 2-tailed.

RESULTS

DISPOSITION AND BASELINE CHARACTERISTICS OF PATIENTS

A total of 1563 potentially eligible subjects were screened. Of these subjects, 1268 patients completed the baseline assessment and underwent randomization; 633 were assigned to receive antipsychotics combined with psychosocial intervention (of whom 29 refused the psychosocial intervention and were excluded from analysis) and 635 to receive antipsychotics alone. Overall, 744 patients (60.0%) completed the 1-year follow-up: 406 (67.2%) in the combined intervention group and 338 (53.2%) in the antipsychotics-alone group (**Figure 1**).

There were no significant differences between study groups with respect to baseline demographic and clinical characteristics. The mean age was 26 years; 55.0% of the patients were male and most patients (84.6%) had a diagnosis of schizophrenia (**Table 2**).

Among the 406 combined-treatment participants who completed the study, the mean (SD) number of sessions attended was 44.2 (4.4) (92.1% of the 48 total sessions), whereas among the 198 combined-treatment partici-

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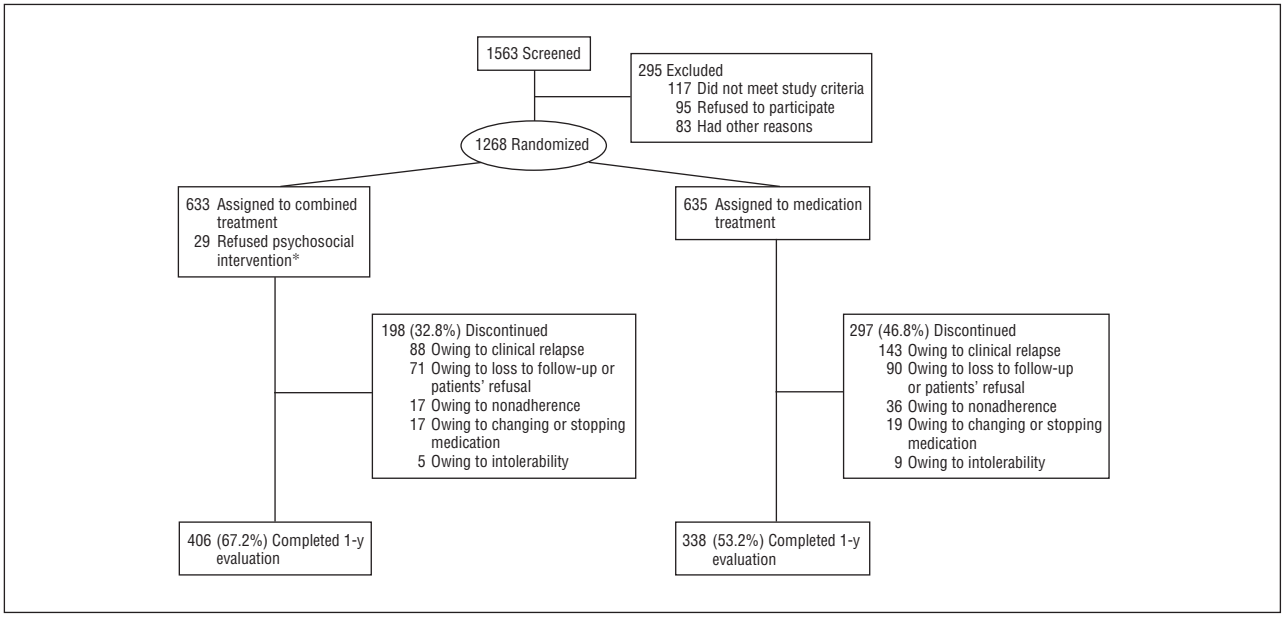

Figure 1. Study flowchart showing the numbers of patients screened for potential inclusion, the reasons for exclusions from randomization, and primary outcome in 1-year follow-up. *These patients were excluded from the final analysis because their follow-up was not carried out.

Table 2. Baseline Demographic and Clinical Characteristics of Randomly Assigned Patients[a]

Characteristic	Combined Treatment (n=633)	Medication Treatment (n=635)
Demographic		
Age, y	26.1 (25.5-26.8)	26.4 (25.7-27.0)
Male, No. (%)	344 (54.3)	354 (55.7)
Marital status, No.(%)		
Married	167 (26.4)	173 (27.2)
Previously married[b]	39 (6.2)	28 (4.4)
Never married	427 (67.5)	434 (68.3)
Education, y	12.2 (11.9-12.5)	12.0 (11.7-12.3)
Clinical		
DSM-IV diagnosis, No. (%)		
Schizophrenia	535 (84.5)	538 (84.7)
Schizophreniform disorder	98 (15.5)	97 (15.3)
PANSS total score	44.7 (43.7-45.7)	45.6 (44.5-46.7)
CGI severity score	2.5 (2.4-2.6)	2.6 (2.5-2.7)
Age at onset, y	23.8 (23.2-24.4)	24.2 (23.4-24.6)
Duration of schizophrenia, mo	24.6 (23.0-26.3)	23.3 (21.7-24.9)
Daily dose of antipsychotic agents, mg/total No. of patients		
Chlorpromazine hydrochloride	332.1 (305.0-359.2)/95	344.9 (319.0-370.8)/94
Sulpiride	720.3 (673.2-767.4)/98	732.8 (683.2-782.4)/97
Clozapine	267.0 (244.0-290.0)/99	269.9 (246.7-293.1)/99
Risperidone	3.5 (3.3-3.7)/111	3.7 (3.4-3.9)/112
Olanzapine	11.9 (10.9-12.9)/79	12.4 (11.1-13.7)/80
Quetiapine fumarate	538.2 (490.2-586.2)/80	524.5 (467.3-581.7)/81
Aripiprazole	18.5 (16.9-20.1)/71	18.5 (16.6-20.4)/72

Abbreviations: PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impressions.
[a] Data are presented as mean (95% confidence interval) unless otherwise indicated. Percentages may not sum to 100 because of rounding.
[b] This category includes patients who were widowed, divorced, or separated.

pants who discontinued or changed treatment, the mean number was 18.1 (4.9) (37.7% of total sessions).

RATES OF TREATMENT DISCONTINUATION

Forty percent of patients in the final analysis (495 of 1239) discontinued their treatment during the 12-month treatment period (32.8% of patients in the combined treatment group and 46.8% of patients in the medication-alone group). The difference between groups in treatment discontinuation for any cause was significant (HR, 0.62; 95% CI, 0.52-0.74; $P<.001$) (**Table 3** and **Figure 2**).

Relapses occurred in 14.6% of patients in the combined treatment group and 22.5% of patients in the medication-alone group. The risk of relapse was lower among

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Table 3. Outcome Measures of Effectiveness in Patients Receiving Combined Treatment or Medication Treatment

Reason for Discontinuation of Treatment	No. (%) Combined Treatment (n=604)	No. (%) Medication Treatment (n=635)	Cox-Model Treatment Comparisons, HR (95% CI)	*P* Value
Any cause[a]	198 (32.8)	297 (46.8)	0.62 (0.52-0.74)	<.001
Any cause except change in medication or intolerability	176 (29.1)	269 (42.4)	0.57 (0.46-0.70)	<.001
Clinical relapse[b]	88 (14.6)	143 (22.5)	0.57 (0.44-0.74)	<.001
Lost to follow-up or patient's refusal	71 (11.8)	90 (14.2)	0.74 (0.54-1.01)	.05
Nonadherence	17 (2.8)	36 (5.7)	0.45 (0.25-0.79)	.006
Changing or stopping medication	17 (2.8)	19 (3.0)	0.84 (0.44-1.62)	.60
Intolerability	5 (0.8)	9 (1.4)	0.66 (0.22-1.99)	.46
Readmission	39 (6.5)	71 (11.2)	0.50 (0.34-0.74)	.007

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Includes clinical relapse, lost to follow-up or patient's refusal, nonadherence, intolerability, and changing or stopping medication.
[b] Includes readmission.

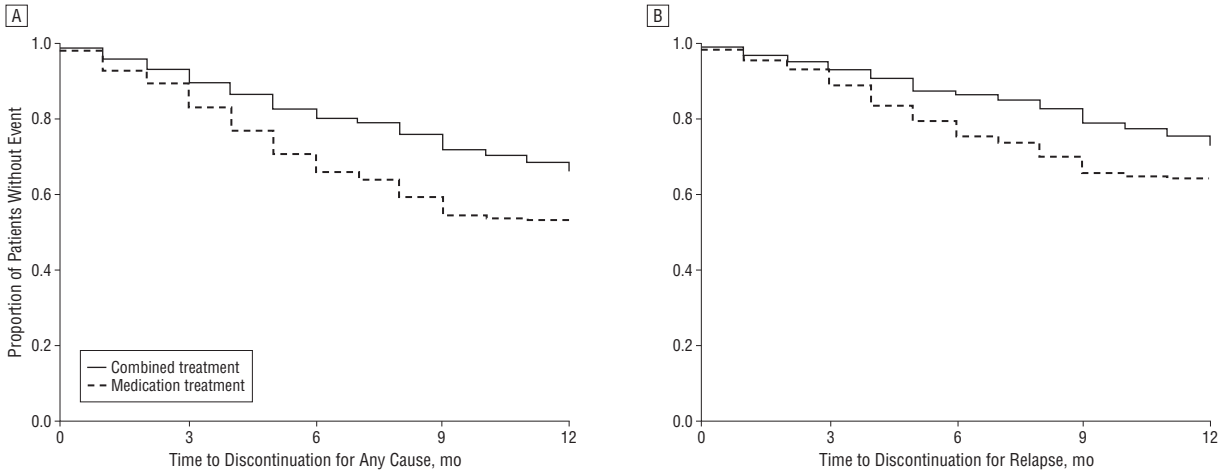

Figure 2. Time to treatment discontinuation because of any cause (A) or relapse (B). A, Kaplan-Meier survival analysis showed a significant difference between the medication treatment group and the combined medication and psychosocial intervention group (log-rank test: χ^2_1=28.85; P<.001). B, Kaplan-Meier survival analysis showed a significant difference between the medication treatment group and the combined medication and psychosocial intervention group (log-rank test: χ^2_1=18.12; P<.001).

patients assigned to combined treatment (HR, 0.57; 95% CI, 0.44-0.74; P<.001) (Table 3 and Figure 2). Nonadherence was noted in 2.8% of patients in the combined treatment group and 5.7% of patients in the medication-alone group; rates of these events were lower among patients assigned to combined treatment (HR, 0.45; 95% CI, 0.25-0.79; P=.006). Readmission occurred in 6.5% of patients in the combined treatment group and 11.2% of patients in the medication-alone group. The risk of readmission was substantially lower among patients assigned to combined treatment (HR, 0.50; 95% CI, 0.34-0.74; P=.007).

We also analyzed all causes of discontinuation for poor outcomes only by excluding intolerance and changing medication (because these events do not always indicate poor outcomes). The results showed that 29.1% in the combined treatment group and 42.4% in the medication-alone group discontinued treatment because of poor outcomes; this difference was statistically significant (HR, 0.57; 95% CI, 0.46-0.70; P<.001).

CHANGES IN SCALE SCORES

The results of the mixed-effects model for repeated-measures analyses of change in psychopathologic behavior and daily functioning assessments between the 2 treatment groups are presented in **Table 4**. Although the analyses used data from the baseline and 3-, 6-, 9-, and 12-month assessments, we present only the baseline and 6- and 12-month mean scores in the table. Analyses showed a significant improvement in total PANSS and ITAQ scores over time in both groups (both F>89.67; both P<.001); however, the change in total ITAQ scores was greater in the combined treatment group than in the medication-alone group (F=25.94; P<.001). Improvements in GAS (F=4.33; P=.002) and ADL (F=12.70; P<.001) scores were also greater over time for the combined treatment group than for the medication-only group. Compared with those in the medication-alone group, those receiving combined treatment showed significantly greater improvement on 4 domains of the SF-36

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Table 4. MMRM Analysis on Clinical and Functioning Outcomes in Patients Receiving CT or MT[a]

Assessment	Mean (95% CI)						Analyses[b]	
	Baseline		6 mo		12 mo		Group × Time Interaction Effect	
	CT (n=580)	MT (n=604)	CT (n=512)	MT (n=472)	CT (n=406)	MT (n=338)	*F*	*P* Value
PANSS	44.6 (43.5-45.7)	45.3 (44.2-46.5)	37.3 (36.5-38.1)	38.8 (38.0-39.7)	34.7 (34.2-35.2)	36.4 (35.7-37.1)	0.41	.81
ITAQ	12.8 (12.4-13.2)	12.7 (12.2-13.1)	17.9 (17.5-18.3)	14.2 (13.7-14.8)	19.5 (19.1-19.8)	15.9 (15.4-16.5)	25.94	<.001
GAS	74.1 (73.2-75.1)	74.2 (73.2-75.1)	79.8 (78.9-80.6)	77.9 (77.0-78.8)	82.9 (82.0-83.7)	80.8 (79.9-81.8)	4.33	.002
ADL	17.2 (17.0-17.4)	17.2 (17.0-17.4)	15.7 (15.5-15.8)	16.6 (16.5-16.8)	15.4 (15.3-15.5)	16.4 (16.3-16.5)	12.70	<.001
SF-36								
Physical functioning	90.8 (89.7-91.8)	90.6 (89.5-91.6)	92.9 (91.8-93.9)	92.3 (91.3-93.2)	95.2 (94.3-96.1)	94.9 (94.1-95.7)	0.12	.87
Role-physical	54.1 (50.8-57.3)	57.3 (54.1-60.6)	67.1 (63.9-70.2)	65.8 (62.5-69.2)	78.1 (74.9-81.3)	73.4 (69.6-77.1)	5.13	.006
Bodily pain	77.2 (74.7-79.8)	78.8 (76.4-81.2)	83.0 (80.5-85.6)	84.4 (81.9-86.9)	89.9 (87.9-91.9)	89.3 (87.0-91.6)	2.80	.06
General health	61.7 (60.3-63.2)	63.5 (62.1-65.0)	67.5 (66.1-69.0)	65.8 (64.2-67.4)	71.3 (69.8-72.8)	67.9 (66.2-69.7)	11.09	<.001
Vitality	59.5 (58.0-61.1)	58.0 (56.4-59.5)	65.6 (64.1-67.1)	60.1 (58.4-61.9)	66.7 (65.0-68.4)	60.5 (58.4-62.7)	5.33	.005
Social functioning	74.5 (72.5-76.5)	74.5 (72.6-76.4)	82.2 (80.4-84.0)	81.2 (79.3-83.0)	86.5 (84.5-88.4)	85.0 (82.9-87.1)	1.00	.37
Role-emotional	57.5 (54.2-60.7)	56.5 (53.1-59.8)	68.0 (64.7-71.2)	63.8 (60.2-67.4)	80.1 (76.9-83.2)	72.1 (68.1-76.1)	3.98	.02
General mental health	65.2 (63.8-66.6)	64.5 (63.2-65.8)	69.1 (67.7-70.6)	67.2 (65.8-68.6)	71.9 (70.4-73.5)	70.2 (68.5-71.8)	1.57	.21

Abbreviations: ADL, Activities of Daily Living scale; CI, confidence interval; CT, combined treatment; GAS, Global Assessment Scale; ITAQ, Insight and Treatment Attitudes Questionnaire; MMRM, mixed-effects model for repeated measures; MT, medication treatment; PANSS, Positive and Negative Syndrome Scale; SF-36, 36-Item Short Form Health Survey.

[a] Analyses are based on MMRM in unstructured variance matrix. Baseline values were included as covariates.

[b] Analyses used data from the baseline and 3-, 6-, 9-, and 12-month assessments; only the baseline and 6- and 12-month results are presented in the table.

Table 5. Safety Outcomes of Patients Receiving Combined Treatment or Medication Treatment in 1-Year Follow-up

Safety Measure	No. (%)		χ^2 Test[a]	*P* Value
	Combined Treatment (n=633)	Medication Treatment (n=635)		
Adverse events				
Extrapyramidal symptoms	135 (21.3)	142 (22.4)	0.20	.66
Hypersomnia, sleepiness	202 (31.9)	216 (34.0)	0.64	.43
Dry mouth, constipation, urinary hesitancy	277 (43.8)	301 (47.4)	1.70	.19
Menstrual irregularities[b]	46 (15.9)	47 (16.7)	0.07	.79
Dizziness	76 (12.0)	82 (12.9)	0.24	.63
Insomnia	35 (5.5)	50 (7.9)	2.79	.10
Weight gain >7% from baseline to last observation	149 (23.5)	132 (20.8)	1.39	.24
Medication added				
Lithium carbonate/anticonvulsants	15 (2.4)	20 (3.1)	0.72	.40
Antidepressants	49 (7.7)	58 (9.1)	0.80	.37
Anxiolytics	35 (5.5)	40 (6.3)	0.34	.56
Anticholinergic agents	161 (25.4)	176 (27.7)	0.85	.36
β-Adrenergic receptor antagonists	41 (6.5)	54 (8.5)	1.88	.20
Other drugs	41 (6.5)	40 (6.3)	0.02	.91

[a] χ^2 for categorical variables.

[b] Percentages are based on the number of female patients: 289 in the combined treatment group and 281 in the medication treatment group.

(role-physical, general health, vitality, and role-emotional; all $F \geq 3.98$; all $P \leq .02$).

In addition, a significantly higher proportion of patients receiving combined treatment obtained employment or accessed education (30.1% in the combined treatment group vs 22.2% in the medication-alone group; $\chi^2 = 10.09$; $P = .001$).

ADVERSE EVENTS

There were no significant differences in the frequency and types of adverse events reported between the 2 groups (all $P > .05$; **Table 5**). The treatment group effect at the end of treatment (determined by analysis of variance with the baseline value as a covariate) was not significant for the dose of antipsychotic medication ($P = .55$). There were no differences between the 2 groups in the rates or types of medications added during the study (all $P > .05$; Table 5).

COMMENT

Treatment of schizophrenia should focus on improving real-world effectiveness outcomes, including functional capacity and health-related quality of life. This study was designed to provide information on the effect of psychosocial intervention on outcome in early-stage schizophrenia, in particular on functional outcome in real-world practice. We found that combined treatment improved medication adherence, risk of relapse and hos-

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pital admission, insight, quality of life, and social/occupational functioning.

Treatment discontinuation in patients with schizophrenia is strikingly common; the Clinical Antipsychotic Trials of Intervention Effectiveness study reported that 74% of patients discontinued their medications during the 18-month study,[2] and the European First Episode Schizophrenia Trial reported that an average of 42% had discontinued their medications at 1-year follow-up.[44] Discontinuing medication is associated with symptom exacerbation, relapse, increased hospitalization, and poor long-term course of illness.[45,46] Our study showed a lower rate of medication discontinuation than the above-mentioned studies. One reason could be that our psychosocial intervention reduced the risk of treatment discontinuation and improved insight and medication adherence; another reason could be that family members are more involved in patients' care in China, similar to other Asian or developing countries. This kind of family involvement and support could further reduce medication discontinuation rates and subsequently improve outcomes. Another potential reason for better outcomes in the combined treatment group is that medication and psychosocial treatments occurred on the same day each month for patients, allowing the psychiatrists and other care providers to reinforce the importance of participation in all components of treatment.

Prevention of relapse is the cornerstone to improving all areas of long-term outcome and achieving long-term improvements in quality of life and level of functioning. The risks of relapse and hospital admission were significantly lower in the combined treatment group than in the medication-alone group in this study.

Improvements in quality of life represent evidence of a good treatment outcome for patients with schizophrenia.[47,48] After 12 months of treatment, more improvements in quality of life were seen in patients who received combined treatment. Better quality of life outcomes in the combined treatment group were demonstrated not only in mental health domains but also in physical health domains, suggesting that combined treatment may afford the best combination of effectiveness and improved quality of life.

Social outcomes reflect how patients live, function in society, and perform their various roles (eg, having a job, going to school, or having friends). Our study showed that a significantly higher proportion of patients receiving combined treatment obtained employment or accessed education. Thus, the findings support the results from previous studies that patients with schizophrenia receiving combined treatment had better outcomes.[12,13,49-52] In particular, integrating a comprehensive therapy with medication treatment in patients with early-stage schizophrenia before the disease becomes chronic and disabling could improve long-term outcomes.

Psychoeducation, family intervention, skills training, and cognitive behavior therapy have proved to be effective in treating people with schizophrenia.[5,7-10,31,52] To our knowledge, this is one of a very few studies to take this integrated intervention approach and address outcome as a whole, with the goal of improving overall outcome in patients with early-stage schizophrenia. Our once-monthly comprehensive psychosocial intervention approach is different from the common therapy model used in the United States and other western countries. Although this study cannot indicate whether this intensive therapy model can be applied in other countries, it did provide evidence that the model was practical and showed better efficacy than medications alone in improving overall outcome for patients with early-stage schizophrenia. This result may be particularly informative to Asian, African, or Latin American countries, where patients with schizophrenia tend to live with their families and family members are often involved in patient care.

This study has several limitations. First, this was a 12-month trial; a longer-term randomized clinical trial would contribute substantially to understanding the longer-term effects of psychosocial intervention on outcomes. Second, although measures were taken to maintain the blinding, it is not known how effective the blinding was. However, several outcome measures were not vulnerable to bias, such as rehospitalization, loss to follow-up, and treatment nonadherence. Third, although the combined psychosocial intervention showed better overall efficacy than medications alone, we do not know whether the effects of the combined intervention were equally attributable to all the modules.

In summary, our study suggests that combined treatment in patients with early-stage schizophrenia reduces the rate of treatment discontinuation and risk of relapse. It also improves insight, adherence to treatment, quality of life, and social functioning. Integrating comprehensive therapy with medication treatment in the early stage of schizophrenia is critically important and should be recommended as the standard of care.

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