Antipsychotic Combination with Psychosocial Intervention on Outcome of Schizophrenia (ACPIOS): Rationale and Design of the Clinical Trial

Xiaofeng Guo,[1] Jingping Zhao,[1] Zhening Liu,[1] Jinguo Zhai,[1] Zhimin Xue,[1] Jindong Chen[1]

Abstract

Effective, long-term treatment of schizophrenic patients has many remaining unsolved problems. Pharmacotherapy alone is insufficient to prevent relapses or to ensure recovery from functional disabilities in the illness course. In an attempt to improve the long-term outcome for individuals with schizophrenia, there is a growing interest in psychosocial interventions as an adjunct to facilitate recovery from an initial episode of psychosis and reduce the long-term disability resulting from schizophrenia. The aim of the Antipsychotic Combination with Psychosocial Intervention on the Outcome of Schizophrenia (ACPIOS) project is to compare antipsychotic medication combination with psychosocial intervention to antipsychotic medication alone on the outcome of schizophrenia. A total of 1,400 patients with ages ranging between sixteen and fifty years who meet the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for schizophrenia and schizophreniform disorder for not more than five years are randomly assigned to either of the above two treatments. Relapse rates and the duration time from the start of treatment to the first relapse are recorded as a measure of the primary effectiveness of the respective treatment regimes. The study will be completed by mid-2008, and it is expected that the results will yield relevant clinical information on how antipsychotic combination with psychosocial intervention affects the outcome of schizophrenia. This paper sets out the rationale and the design of the trial.

Key Words: Antipsychotic, Outcome, Psychosocial Intervention, Schizophrenia

Introduction

Schizophrenia is one of the most disabling of all mental diseases. The incidence of occurrence among the general population is one in one hundred, and approximately eighty percent of sufferers will experience chronic or relapsing symptoms (1). Statistically, schizophrenia is among the world's top ten disabling diseases (2). The majority of individuals with schizophrenia has a poor long-term outcome (e.g. chronic psychosis, a deteriorating course, or suicide) which results in great personal suffering and social cost (3-8). Conventional and new-generation antipsychotic drugs have been shown to be effective on treatment and relapse prevention, and they are now the mainstay of therapy for patients with schizophrenia. However, most patients, even patients with a good response to medication, would likely continue to suffer from disabling residual symptoms, impaired social functioning, and high risk of relapse despite treatment continuation. Therefore,

[1]*Institute of Mental Health, The Second Xiangya Hospital, Central South University, Hunan, P.R. China*

Address for correspondence: Jingping Zhao, MD, Institute of Mental Health, The Second Xiangya Hospital, Central South University, Changsha 410011, Hunan, P.R. China
Phone: +86-731-536-0921; Fax: +86-731-536-0921;
E-mail: zjpliu6@public.cs.hn.cn

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pharmacotherapy alone is not sufficient to prevent relapses or to ensure functional recovery from acute psychosis. There is a growing interest in psychosocial interventions as a means to improve recovery from an initial episode of psychosis and reduce the long-term disability related to schizophrenia (9).

Previous research has provided support for the additive effectiveness of psychosocial interventions delivered in combination with pharmacological treatment (10). With the addition of a psychosocial treatment, greater improvement is brought to an effective outcome than with pharmacological treatment alone. For instance, family intervention reduces relapse rate; cognitive behavior treatment reduces positive symptoms (11, 12); and social skills training improves social competence (13).

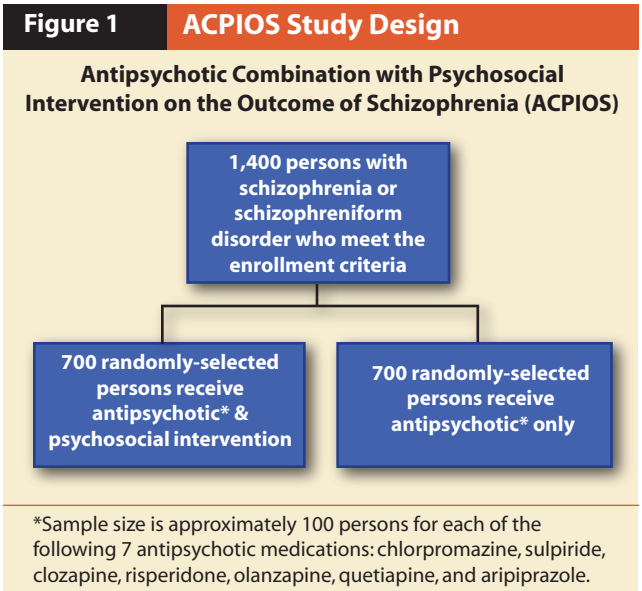
In order to improve the long-term outcome of patients with schizophrenia, recent research has focused on early identification and intervention for psychosis. Most clinical and psychosocial deterioration in schizophrenia occurs within the first five years of the onset of the illness, suggesting that this is the critical period for treatment initiation (14, 15).

There are quite a few important achievements in studies on outcome of schizophrenia over recent years, including the European Schizophrenia Outpatient Health Outcomes study (SOHO) (16), the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (17), the European First Episode Schizophrenia Trial (EUFEST) (18), and the Danish National Schizophrenia Project (Danish OPUS trial) (19). SOHO, EUFEST, and CATIE stress comparing treatment with first- and second-generation antipsychotics in first-episode or chronic patients. OPUS is the first large-scale, randomized clinical trial of integrated treatment versus standard pharmacological treatment for patients with first-episode psychosis.

In P.R.China, we are embarking on a study named the Antipsychotic Combination with Psychosocial Intervention on the Outcome of Schizophrenia (ACPIOS), which is an eighteen-month, randomized clinical trial comparing antipsychotic combination with psychosocial intervention to antipsychotic treatment alone on patients with stable schizophrenia (Figure 1). The goals of the ACPIOS study are as follows: 1) to compare antipsychotic medication combination with psychosocial intervention to antipsychotic treatment alone on the outcome of schizophrenia; 2) to compare the long-term effectiveness and tolerability of first- and second-generation antipsychotics in schizophrenic patients; 3) to establish a set of psychosocial intervention strategies for use in China.

In this paper we discuss the rationale and design of ACPIOS. Up to this point, it is one of the largest randomized trials investigating the effectiveness of antipsychotic drugs in combination with psychosocial intervention on the therapeutic outcome of schizophrenia.

Figure 1 ACPIOS Study Design



*Sample size is approximately 100 persons for each of the following 7 antipsychotic medications: chlorpromazine, sulpiride, clozapine, risperidone, olanzapine, quetiapine, and aripiprazole.

Methods

Objectives

Consenting sixteen- to fifty-year-old patients are enrolled into the study with the following prerequisites: 1) meeting the structured clinical interview for *DSM-IV* criteria for schizophrenia, or schizophreniform disorder, for not more than five years; 2) being confirmed to be clinically stable by the investigator (the total score ≤60 on the Positive and Negative Syndrome Scale (PANSS) (20) or a decrease of fifty percent from acute period in the total score on PANSS; 3) taking maintenance therapy with any one of the following seven oral antipsychotics: chlorpromazine, sulpiride, clozapine, risperidone, olanzapine, quetiapine, and aripiprazole.

Patients are excluded from the trial for any of the following reasons: 1) meeting *DSM-IV* criteria for another Axis I diagnosis of schizoaffective disorder, mental retardation, pervasive developmental disorder, delirium, dementia, amnesia, or other cognitive disorders; 2) having a serious or unstable medical illness; 3) requiring more than one antipsychotic or long-acting injectable medication to maintain treatment adherence; 4) women who are pregnant or breast-feeding. Before starting the study, participants will provide written consent after the procedures have been fully explained. (See Table 1 for a summary of enrollment criteria.)

Design and Duration

The study is a randomized and naturalistic multicenter study with a minimum intervention period of eighteen months and assessments of participants at baseline, three months, six months, and every three months thereafter. An additional visit will be made in case of: 1) discontinuing and/or changing antipsychotic drugs; 2) an additional antipsychotic drug for at least fifteen days in a three-month

Table 1 Enrollment Criteria

Key Inclusion Criteria
- consenting 16- to 50-year old patients
- meets the structured clinical interview for *DSM-IV* criteria for schizophrenia, or schizophreniform disorder, for not more than 5 years
- evaluated as clinically stable by the investigator (total score ≤ 60 on the PANSS or a decrease of 50% from acute period in total PANSS score)
- on maintenance therapy with any one of the following seven oral antipsychotics: chlorpromazine, sulpiride, clozapine, risperidone, olanzapine, quetiapine, or aripiprazole
Key Exclusion Criteria
- meets *DSM-IV* criteria for another Axis I diagnosis of schizoaffective disorder, mental retardation, pervasive developmental disorder, delirium, dementia, amnesia, or other cognitive disorders
- has a serious or unstable medical illness
- requires more than one antipsychotic or long-acting injectable medication to maintain treatment adherence
- women who are pregnant or breastfeeding

interval; 3) hospitalization and/or relapse (for definitions see below). Patients who meet any of these three criteria will be considered treatment failures, and any of their study outcomes will no longer be followed. Causes of treatment discontinuation will be assessed, including lack of safety, lack of efficacy, poor medication adherence, or patient decision.

Approximately 1,400 participants will be enrolled, with about 140 participants enrolled at various sites (see below). The sample size for each of the seven antipsychotic drug groups is about two hundred individuals, who are randomly selected to receive either antipsychotic drugs in combination with psychosocial intervention or to receive only antipsychotic drugs. Group assignment is based on a 1:1 randomization scheme balanced by sites; therefore, seven hundred participants will be treated by antipsychotic drugs in combination with psychosocial intervention, and the other seven hundred participants will be treated by antipsychotic drugs alone.

Treatments

Pharmacological Treatments

Patients who initiate or change to one of the study's seven antipsychotic medications are candidates. After patients agree to participate in the study and give informed consent, they enter a one- to two-month pretreatment period. During this time, patients undergo a battery of assessments that include the structured clinical interview for *DSM-IV* and PANSS. If patients are found to meet the aforementioned criteria for study participation, they undergo the baseline assessments which include: clinical psychopathology, side effects, compliance, social function, neurocognitive function, quality of life, and family/career burden. Patients remain on the same antipsychotic medication on which they started the study. The dose ranges of medication are as follows: chlorpromazine at 200-800 mg/d, sulpiride at 200-1500 mg/d, clozapine at 100-500 mg/d, risperidone at 2-6 mg/d, olanzapine at 5-20 mg/d, quetiapine at 150-800 mg/d, and aripiprazole at 5-30 mg/d. Patients are visited monthly by at least one treating physician during the study. All medications are administered orally within the prescribed dose ranges at the treating physician's discretion. Patients in the antipsychotic-only group will not be provided any type of psychotherapy.

Concomitant Therapy

Mood stabilizers, benzodiazepines, antidepressants, and anticholinergic medications are permitted, but daily doses should be recorded throughout the study.

Psychosocial Intervention

One-half of the research participants are randomly assigned to psychosocial intervention for twelve months, which is carried out independently of the assessors who are kept blind of treatment allocation. The psychosocial intervention strictly follows a detailed treatment manual designed by the principal investigators and is based on past studies (21-25). At the beginning of the study, the principal investigators provide initial training in the procedure and monthly supervision of videotaped sessions. Psychosocial interventions are aimed at improving the patients' and families' understanding of the illness; decreasing the burden of illness on the families; maximizing treatment adherence, minimizing relapse; and, improving social function and study retention.

Psychosocial interventions (see Table 2 for summary) provided to each patient in the psychosocial group include the following:

Psychoeducation

All participants are given a monthly group educational plan. The purpose of psychoeducation is to increase patients'

Table 2 Components and Aims of Psychosocial Intervention

Component	Aim
Psychoeducation	Increase patients' and caregivers' knowledge and understanding of the illness and treatment.
Family Intervention	Improve behavioral problem solving, family support, and crisis management skills.
Skills Training	Promote independent functioning in daily living.
Cognitive-Behavioral Therapy (CBT)	Treatment of auditory hallucinations and delusions, associated symptoms and problems, and relapse prevention.

and caregivers' knowledge and understanding of the illness and treatment. Each group is composed of six to eight patients, their caregivers, and two therapists who provide the intervention. Each session lasts sixty minutes, and includes teaching patients and caregivers about the symptoms treatment and course of mental illness; affords family members the opportunity to ask questions about psychiatric disorders and treatment options; and, provides a forum in which to discuss concerns and obtain support from the group in order to reduce the stigma of mental illness.

Family Intervention

Multiple-family group treatment is given to all patients and their families. Each multiple-family group is composed of six to eight families and two therapists. The complete intervention lasts twelve months for each cohort, with monthly meetings. The elements of family interventions are behavioral problem solving, family support, and crisis management. Each session lasts sixty minutes and includes developing collaboration with the family; socializing about non–illness-related topics; 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 early-detect and intervene in crises.

Skills Training

Skills training involves life-skills training and social-skills training in groups of six to eight patients and two therapists. The intervention lasts twelve months for each cohort with monthly sixty-minute meetings. Life-skills training is intended to promote independent functioning in daily living. These programs include: managing money, organizing and running a home, domestic skills, and personal self-care. Social-skills training focuses on: medication, coping with symptoms, conversation, daily life action, and problem-solving social skills. The training includes teaching complex interpersonal skills by breaking the targeted behaviors into component steps and systematically using modeling, behavioral rehearsal, positive and corrective feedback, and "live" practice to shape the acquisition and generalization of skills.

Cognitive-Behavioral Therapy (CBT)

All patients in the study are assigned to group CBT. Sixty-minute group CBT is given once monthly. Every group is composed of six to eight patients and two therapists. CBT is primarily directed at the treatment of auditory hallucinations and delusions, associated symptoms and problems (i.e. anxiety, depression, self-esteem), and relapse prevention. For some patients with psychotic symptoms remitted, CBT is aimed at relapse prevention, treatment of associated problems, and enhancing medication adherence. Treatment involves the following elements: assessment and engagement, education, and building a therapeutic alliance; functional analysis of key symptoms, leading to formulation of a problem list; development of a normalizing rationale for the patients' psychotic experiences; exploration and enhancement of coping strategies; acquisition of additional coping strategies for hallucinations and delusions; focusing on concomitant-affective symptoms using relaxation training; and, relapse prevention/ keeping well.

Outcome Measures

The outcome variables of schizophrenia are measured, including clinical psychopathology, side effects, compliance, social function, neurocognitive function, quality of life, and family/career burden. Cost analysis is involved as well.

ACPIOS' primary outcome variable is relapse rates and duration to first relapse. Relapse is defined by any one of the following (26): psychiatric hospitalizations; an increase in the level of psychiatric care and an increase of twenty-five percent from baseline in the total score on PANSS (20), or an increase of ten points if the baseline score is 40 or less; deliberate self-injury; suicidal or homicidal ideation that is clinically significant in the investigator's judgment; violent behavior resulting in clinically significant injury to another person or property damage; or, substantial clinical deterioration, defined as a change score of 6 ("much worse") or 7 ("very much worse") on the Clinical Global Impressions

Scale (CGI) (27). The discontinuation of drug treatment is another primary outcome variable.

Secondary outcome variables are different dimensions of psychopathology in schizophrenia, including: side effects, compliance, subjective attitudes toward medication, social function, neurocognitive function, quality of life, family/career burden, and cost-effectiveness analysis.

The following instruments are selected to measure these secondary outcomes:

The Positive and Negative Syndrome Scale (PANSS) (20, 28-30), the Brief Psychiatric Rating Scale (BPRS) (31), and the Montgomery-Asberg Depression Rating Scale (MADRS) (32) are used to assess psychopathological symptoms. The severity of psychopathology is rated by CGI (27).

Side effects focus on extrapyramidal side effects (EPS), tardive dyskinesia, weight gain, blood glucose, hyperprolactinaemia, and sexual dysfunction. Treatment Emergent Symptom Scale (TESS) (27) and a Rating Scale for Extrapyramidal Side Effects (RSESE) (33) are used. Each participant's pulse, breath, and blood pressure are assessed regularly. To evaluate the effect of antipsychotic treatments on weight gain, fasting blood glucose level, waist-hip ratio (WHR), and body-mass index (BMI) are collected regularly.

Treatment compliance is measured using the Drug Attitude Inventory with ten questions (DAI-10) (34, 35), and information about appointment compliance is recorded in follow-up visit records.

Poor insight is common in patients with schizophrenia, and studies have demonstrated associations between lack of insight and poorer treatment compliance. The Insight and Treatment Attitudes Questionnaire (ITAQ) (36) is used to measure awareness of illness and insight into need for treatment in patients with schizophrenia.

Social function is measured by the Disability Assessment Schedule (DAS) (37) and the Activities of Daily Living Scale (ADL) (38). Quality of life is measured by the Short Form 36 Health Survey Questionnaire (SF-36) (39).

Tests for neurocognitive functioning include: Computerized Continuous Performance Test (40), Computerized Wisconsin Card Sorting Test (41), Trail Making Test A+B (42), a part of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) including Digit Span Test and Digit Symbol Test (43), and Visual Reproduction subtest of the Wechsler Memory Scale-Revised (44).

Family/career burden is measured by Family Burden Scale (FBS) (45) and Caregiver Burden Scale (CBS) (46, 47).

Cost analysis involves direct and indirect costs. Direct costs include the cost of medications and service use. Indirect costs include disability payments friction costs, loss of earned income, accommodation data, and family burden in terms of time costs.

Statistical Methods and Analytic Plan

The null hypothesis investigated is that there will be no differences between antipsychotic drug combination with psychosocial intervention versus antipsychotic drug alone with regard to relapse, time to first relapse, psychotic and negative symptoms, treatment adherence, quality of life, cognitive function, and social function. The analysis will be conducted on the intent-to-treat population.

The sample sizes are selected to make possible the detection of a twenty percent difference in relapse rates after two years with eighty percent power and a two-tailed level of significance of 0.05. The sample sizes must be increased less than twenty percent to account for dropout for reasons other than relapse, so seven hundred patients per treatment group is of sufficient power.

The primary analysis will consist of a comparison of relapse rates and time to first relapse between antipsychotic-only treatment group and antipsychotic drug combination with psychosocial intervention treatment group from the beginning of the trial. Regarding time to the first relapse, the start point is the time of randomization and the endpoint is the moment that the patient meets one of the relapse criteria. The rates of discontinuation drug treatment and the time to the discontinuation will be analyzed as other primary outcome variables.

The primary objective of this study will be examined with survival analysis, both Kaplan Meyer Survival Analysis and uni- and multivariate Cox Proportional Hazards Analysis (48), and differences in time to relapse between treatment groups are analyzed with use of a logrank test with control for sites also.

Descriptive statistics will be provided for all data broken down by treatment group, by visit, and by site. Continuous variables will be described by mean, standard deviation, range, and number of observations. Discrete variables will be described by frequencies and percentages. All statistical tests will be carried out as two-tailed tests, and alpha (level of significance) is set at 5%. Differences in continuous variables will be tested with analysis of variance, with treatment sites included as covariates. We will use the Mann-Whitney's U Test to test differences in continuous data with skewed distribution. Discrete variables are analyzed with ChiSquare or Fisher's Exact Tests. The analysis in repeated measurements model with unstructured variance matrix will be performed, where applicable, for analysis of the secondary objectives (49, 50). This approach assumes that the distribution of miss data could be estimated from the information from the previous interviews.

In the second step of analysis, the seven antipsychotic drug groups will be compared. It is assumed that significant

differences will be found among the seven antipsychotics in primary outcome variables including relapse rate, time to first relapse, discontinuation rates and time to discontinuation, and secondary outcome variables including psychotic and negative symptoms, side effects, treatment adherence, quality of life, cognitive function, and social function.

Quality Control

There are nine sites participating in the study which are led by the Second Xiangya Hospital of the Central South University, the trial originator. The participating sites are: Beijing Anding Hospital, Nanjing Brain Hospital, Shanghai Mental Health Centre, Jiangxi Province Mental Health Hospital, Guangzhou Brain Hospital, Chongqing Mental Health Centre, Henan Province Mental Health Hospital, Huaxi Hospital of Sichuan University, and Hunan Province Brain Hospital.

The Second Xiangya Hospital of the Central South University coordinates monitoring and data entry. A study start-up meeting is an efficient strategy to initially familiarize site staff with the protocol and provide study procedure training. The trial originator provides instructional materials to all study sites, and organizes an initial five-day training event that occurs prior to the implementation of the trial. Reliability assessments of the major rating scales are carried out. The originators of the intervention provide initial training in the procedure and monthly supervision of videotaped sessions.

Summary and Outlook

This article has described the rationale, aims, and design of ACPIOS, and the method for evaluating the effectiveness of antipsychotic combination with psychosocial intervention, and the long-term effectiveness and tolerability of first- and second-generation antipsychotics.

As of the date of submission of this manuscript, in total 1,400 patients have been enrolled in the trial. In total, seven hundred patients have already completed the twelve-month follow-up, with ten percent of the patients lost to follow-up and ninety percent still in active follow-up. The trial will finish by mid-2008. It is expected that results will yield relevant clinical information on how antipsychotic combination with psychosocial intervention affects the outcome of schizophrenia.

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