

Chapter 23. Schizophrenic Disorders

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I. INTRODUCTORY REMARKS

Psychotic disorders are personality and thought disorders that are associated with emotional and behavioral impairments (1). Schizophrenia is a psychotic disorder that is accompanied by impairments in speech patterns, inability to process information, delusions, and hallucinations (1). Schizophrenia consists of positive and negative symptoms (1). Increased activity, agitation, delusions, and hallucinations characterize positive symptoms (1). The mechanism by which these symptoms are manifest is through an increase in dopaminergic activity in the brain. Negative symptoms, on the other hand, are characterized by a decrease in activity, loss of pleasure, withdrawal from social interactions, a decrease in dopaminergic activity in the cerebral cortex, and an increase in dopaminergic activity in the striatum (1). The diagnostic criteria of Schizophrenia according to the DSM-IV include that the patient's illness has to be continuous for at least six months and an occurrence of at least one psychotic phase followed by a residual phase (2). Pharmacological treatments of Schizophrenia include the use of first generation antipsychotics, such as haloperidol, and second generation antipsychotics, such as clozapine (3). First generation antipsychotics are potent antagonists of the dopamine 2 receptors in the striatum. They also block serotonergic, cholinergic, adrenergic, and histaminergic receptors (3). The wide array of affinity of these drugs to various receptors leads to side effects including extrapyramidal effects (sedation), tachycardia, dry mouth, blurred vision, gastrointestinal problems, sexual dysfunction, and orthostatic hypotension, Parkinson's like syndrome, tardive dyskinesia, dystonia, akathisia, and neuroleptic malignant syndrome (1). These side effects are dose-related unlike the efficacy, which reaches a plateau after a certain dose. All first generation (typical) antipsychotics exhibit the same efficacy for the treatment of positive symptoms of schizophrenia, but their effect on negative symptoms has yet to be determined. Second generation (atypical) antipsychotics were developed for patients who are resistant to treatment with first generation antipsychotics (1). They have been shown in many studies to exhibit higher efficacy and slightly better tolerability (better safety profile) than first generation drugs in the treatment of schizophrenia (1). Many atypical antipsychotics block the dopamine 4 receptors in the cerebral cortex. They also have affinity for the serotonin 2 receptors and the dopamine 2 receptors (1). The better tolerability that atypical drugs exhibit accounts for the lower risk of extrapyramidal symptoms; however, adverse effects on the cholinergic and adrenergic systems still exist (1). As a result, an antipsychotic drug is required that exhibits high efficacy for the treatment of both positive and negative symptoms of schizophrenia. In addition, the antipsychotic drug must exhibit a wide therapeutic index, no extrapyramidal side effects, and very low cholinergic and adrenergic effects.

In this chapter, a double blind, placebo controlled, parallel-group study design will be used to test the efficacy and safety of investigational drug YYY versus placebo in patients diagnosed with schizophrenia. Previous clinical studies have shown that drug YYY is a highly potent dopamine 4 receptor antagonist, has no sedative effect, has a fast onset of action, and requires once daily dosing. In this study design, these properties of the drug will be better characterized and its efficacy and safety will be determined. The example of the study design illustrated in this chapter is most applicable to trials evaluating antipsychotic drugs intended to be used in patients with schizophrenia.

II. PHASE II STUDIES FOR REGISTRATION OF NEW ANTIPSYCHOTIC DRUGS

II.1. Outline of a typical development plan

This study will examine the efficacy and safety of drug YYY in men and women diagnosed with schizophrenia according to the DSM-IV. All patients enrolled in the study meeting inclusion/exclusion criteria and that give consent will be randomly assigned to receive one oral daily dose of drug YYY or placebo for 6 months. A long-term trial has been chosen for this study since the cholinergic and adrenergic side effects usually take 3 to 6 months to appear. Efficacy and safety measures are going to be performed

at weekly intervals up to the end of week 12, and then at 2-week intervals up to week 24. The study will be randomized, double blind, placebo-controlled and patients will come back for two follow-up assessments.

II.2. Long-term studies

II.2.a. Study Objectives

Primary Objectives

- a. To compare the efficacy of drug YYY treatment versus placebo in reducing the positive and negative symptoms of schizophrenia.
- b. To compare the safety of drug YYY treatment versus placebo

Secondary Objectives

- a. To determine the onset of the antipsychotic action of drug YYY
- b. To determine the duration of the antipsychotic effect of drug YYY
- c. To determine the peak antipsychotic effects of drug YYY

II.2.b. Primary Endpoints

Rating scales will be administered to assess the following dependent variables:

- a. Structured Clinical Interview for DSM-IV to diagnose patients with schizophrenia.
- b. Brief Psychiatric Rating Scale (BSRS) to determine the severity of the disorder and positive and negative symptoms. It is a 16-item scale, which includes 7 points for severity scale, 5 points for positive symptoms, 2 points for negative symptoms, and 9 general symptom points. Patients with schizophrenia score ≥ 33 points out of 112 (4). Positive and Negative Syndrome Scale (PANSS) which also determines the severity of schizophrenia and more specifically deals with the positive and negative symptoms associated with schizophrenia. It is a 30-item scale, which includes 7 points that measure positive symptoms, 7 points for negative symptoms, and 16 points for general psychopathology symptom measure. A schizophrenic patient would typically score 91 at beginning of trial (4).
- c. Clinical Global Impression Scale (CGI) is used to assess treatment response in psychiatric patients. It is a 3-item scale that measures the severity of the illness (7-point scale), global impairment (7-point scale), and efficacy index (4-point scale). This scale is taken at baseline and repeated after drug exposure in order to compare results and assess efficacy (4).
- d. Simpson Angus Scale (SAS) detects any drug induced parkinsonism and extrapyramidal side effects. It evaluates the presence and severity of the symptoms using a 10-item rating scale (4).
- e. Barnes Akathisia Scale (BAS) is a 4-item scale that detects the presence and severity of any drug induced akathisia. The scale measures the objective and subjective effects such as restlessness and awareness of restlessness respectively (4).
- f. Extrapyramidal Symptom Rating Scale (ESRS) is a 12-item scale that detects the presence of drug induced parkinsonism like symptoms, akathisia, dyskinesia, and dystonia (4).
- g. Abnormal Voluntary Movement Scale (AIMS) is a scale that detects the patient's movements by providing certain positions in which the patients have to rotate his/her body and the psychiatrists assess whether abnormal facial or body movements exist (4).

Responders to the antipsychotic drug YYY versus placebo, where a response is defined as:

- a. R = a reduction from baseline (visit 1) during (weeks 1 – 24) and post treatment (2 follow-up sessions) as measured by the BSRS.
- b. R = a reduction from baseline (visit 1) during (weeks 1 – 24) and post treatment (2 follow-up sessions) as measured by the PANSS.

- c. R = a reduction in the CGI scale scores on weeks 1-24 compared to baseline will indicate the presence of drug efficacy. The higher a reduction in the score, the more efficacious the drug is considered.
- d. R = an increase in the SAS scale scores on weeks 1- 24 compared to baseline will indicate a presence of parkinsonism-like adverse effect.
- e. R = an increase in the BAS scale scores on weeks 1 – 24 compared to baseline will indicate the presence of akathasia.
- f. R = an increase in the ESRS scale scores on weeks 1 – 24 compared to baseline will indicate the presence of extrapyramidal adverse effects.
- g. R = an increase in the AIMS scale score on weeks 1 – 24 compared to baseline will indicate the presence of abnormal voluntary movements.

II.2.c. Secondary Endpoints

- a. The time of onset of a consistent decrease in schizophrenic symptoms as measured by the CGI compared to baseline.
- b. The treatment day during which the greatest reduction in the schizophrenic symptoms is present as measured by the PANSS.
- c. The number of patients that achieve a BSRS < 33 and a PANSS < 91 by the end of the study period.
- d. Time of onset of any adverse effect as measured by the SAS, BAS, ESRS, and AIMS scales.
- e. Severity of the adverse effects (if developed) as measured by the SAS, BAS, ESRS, and AIMS scales.
- f. Number of subjects that drop out because of the development of adverse effects.

Adverse effects are measured by changes in blood pressure, heart rate, GI motility, and abnormal laboratory tests (blood and liver).

II.2.d. Study Design

This is a double blind, randomized, placebo-controlled, parallel-group study. There will be 2 groups in this study, schizophrenic patients and a healthy control group. Patients in each group will receive either a single dose of drug YYY or a single dose of placebo randomly once daily for 24 weeks. The number of patients receiving drug YYY will equal the number of patients receiving placebo within each group. The antipsychotic effect of drug YYY will be measured using various questionnaires (discussed below). Objective measures, such as blood pressure, will also be obtained. The results will be compared and analyzed between and within groups.

Screening for Eligibility (Visit 1, One week before start of the study)

Subjects will be interviewed to ensure suitability for study participation a week before the commencement of the study. The following will be required to assess eligibility:

- a. Written informed consent.
- b. Structured Clinical Interview for DSM-IV to assess psychiatric status and to rule out dependence on psychoactive substances.
- c. Current level of schizophrenia (Brief Psychiatric Rating Scale (BSRS), Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Scale (CGI), Simpson Angus Scale (SAS), Barnes Akathisia Scale (BAS), Extrapyramidal Symptom Rating Scale (ESRS), Abnormal Voluntary Movement Scale (AIMS)). This is the baseline measure to which all upcoming results will be compared.
- d. Brief medical examination (heart rate, blood pressure).
- e. Medical history.
- f. Review of inclusion/exclusion criteria.

- g. Pregnancy test for women.
- h. Blood and urine samples to assess liver function, hematology, biochemistry, and to detect the presence of other psychoactive drugs.
- i. Participants will be provided with a pager number to be used if they experience any serious side effects and a wallet card containing information about participation in this study.
- j. Patients are also given a diary in which they record drug compliance and any side effects that they may experience on a daily basis.

Treatment Phase (Visits 2-19, Months 1-6)

- a. Eligible subjects will attend 24 treatment sessions (weekly intervals up to the end of the 6 months).
- b. Medical examination.
- c. Medication will be dispensed (enough pills to last for the next visit at once daily dosing)
- d. Treatment will consist of 60 minutes sessions with the research assistant.
- e. A psychiatrist will be available for consultation, assessment, and treatment as needed (i.e. adverse drug reaction, increases in severity of anxious symptomatology).
- f. Review Daily Diary forms on which patients record compliance with medication and any side effects that the patient may be experiencing.
- g. At each visit, the BSRS, PANSS, SAS, BAS, ESRS, and AIMS will be completed and subjects will be interviewed regarding concomitant illness and medication use.
- h. Ask patients to return any unused medication in the vial.
- i. Blood will be drawn for trough drug concentrations at 2- week intervals after the start of the study.
- j. Blood and urine will also be collected at 2-week intervals for drug screen, complete biochemistry and hematology analysis.
- k. Subjects will be referred to their family physicians either at the end of the 6 months or if a subject decides to terminate participation in the study.
- l. Individuals who do not respond to drug YYY will be referred to alternate psychiatric treatment or to their family physicians.

Follow-up visits (Visits 20-21, at 8 months and 12 months after treatment)

- a. Review daily diary.
- b. Medical examination.
- c. Psychiatrist: examine any increased schizophrenic symptoms, interview patients for concomitant illness, and examine potential adverse reactions.
- d. Complete questionnaires: BSRS, PANSS, SAS, BAS, ESRS and AIMS.
- e. Blood and urine collection for drug screen, complete biochemistry and hematology analysis.

II.2.e. Planned Sample

Refer to Fleming's Single Stage Procedure Subsection II.2.e. (Planned sample) of the Mood disorders Section in Chapter 20.

II.2.f. Study Population

Male or female over 18 years of age meeting DSM-IV criteria for Schizophrenia and score ≥ 33 on the BSRS and ≥ 91 on the PANSS.

II.2.g. Specific Inclusion Criteria

A subject will be eligible for inclusion in the study only if all of the following criteria apply:

- a. Males or females between 19 to 50 years of age.
- b. Socially stable.

- c. Meet DSM-IV criteria for schizophrenia.
- d. In-patients or out-patients.
- e. Non-smokers.

II.2.h. Specific Exclusion Criteria

Exclusion criteria must take into account the characteristics of the drug (pharmacokinetics, and pharmacodynamics, drug-drug interactions, and adverse effects). Patients will not be eligible to participate in the study if any of the following criteria apply:

- a. If meet criteria for Bipolar Disorder, MDD, Anxiety, or substance abuse/dependence.
- b. Evidence of medical or surgical illness requiring treatment.
- c. History of psychoactive drug dependence or a positive urine test for psychoactive drugs.
- d. Use of medications which may interfere with the study procedures (e.g. SSRIs).
- e. Any clinically significant abnormality evident in biochemistry or hematology test results or in urine analysis requiring further investigation.
- f. Receiving or will receive other investigational drug during the study.
- g. Pregnant or lactating females.

II.2.i. Tools to assess endpoints

The tools used to assess efficacy are shown in the following table.

Variable	Assessment Tools to Measure Variable	Time of Assessment
Diagnosis of Schizophrenia	DSM-IV	Visit 1 (baseline)
Level and Severity of Schizophrenia	BSRS, PANSS, CGI	Visit 1 (baseline)
Reduction in Schizophrenic Symptoms	BSRS, PANSS, CGI	Visits 2-21
Reduction in Positive Symptoms	BSRS, PANSS	Visits 2-21
Reduction in Negative Symptoms	BSRS, PANSS	Visits 2-21
Induction of Extrapyramidal Adverse Effects	SAS, ESRS	Visits 2-21
Time of induction and Severity of Extrapyramidal AE	SAS, ESRS	Visits 2-21
Induction of Parkinsonism-like Symptoms	SAS	Visits 2-21
Time of Induction and Severity of Parkinsonism-like Symptoms	SAS	Visits 2-21
Induction of Akathisia	BAS	Visits 2-21
Time of Induction and Severity of Akathisia	BAS	Visits 2-21
Induction of Involuntary Movements	AIMS	Visits 2-21
Time of Induction and Severity of Involuntary Movements	AIMS	Visits 2-21
Time of onset of a consistent decrease in schizophrenic symptoms	BSRS, PANSS, CGI	Visits 2-21
Time of greatest reduction of Schizophrenic symptoms	BSRS, PANSS, CGI	Visits 2-21
Number of patients achieving BSRS > 33	BSRS	Visits 2-21
Number of patients achieving PANSS > 91	PANSS	Visits 2-21
Drug Compliance	Patient Daily Diaries and Returned Medication	Visits 2-19

The tools to assess safety are described in Subsection II.2.i. (Tools to Assess Safety) of the Mood Disorders Section of Chapter 20.

II.2.j. Specific criteria for early withdrawal and discontinuation

Refer to Subsection II.2.j. (Specific criteria for early withdrawal and discontinuation) of the Mood Disorders Section of Chapter 20.

II.2.k. Data Analysis Method

Refer to Subsection II.2.k. (Data Analysis Method) of the Mood Disorders Section of Chapter 20.

III. REFERENCES

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