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TRIAL DESIGN SUMMARY

Comparative Effectiveness of Antipsychotic Medications in Patients with Schizophrenia

Clinical Antipsychotic Trials of Intervention Effectiveness
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This study is a randomized controlled trial of up to 1600 patients with schizophrenia involving the following medications: perphenazine, fluphenazine decanoate, clozapine, olanzapine, quetiapine, risperidone, ziprasidone and aripiprazole. Patients will be followed for up to 23 months and re-randomized to a new treatment in the event of treatment failure.

SPECIFIC AIMS

1. To determine the long-term effectiveness and tolerability of the newer atypical antipsychotics, relative to each other. This will involve comparing treatment with olanzapine to treatment with risperidone, as well as contrasting treatment with ziprasidone vs. treatment with olanzapine, quetiapine, and risperidone combined.
2. To determine the long-term effectiveness and tolerability of the newer atypical antipsychotics, relative to perphenazine, across the spectrum of schizophrenic illness. We hypothesize that treatment with the newer atypical antipsychotics will be associated with greater long-term effectiveness and tolerability than treatment with perphenazine.
3. To determine, among patients who fail treatment with an initially assigned newer atypical antipsychotic, the long-term effectiveness and tolerability of the newer atypical antipsychotics, relative to clozapine. We expect patients with inadequate resolution of psychopathology, or exquisite sensitivity to EPSE, to preferentially select this Phase 2 trial. We hypothesize that treatment with clozapine will be associated with greater long-term effectiveness and tolerability than treatment with a newer atypical drug other than the one the patient initially received.
4. To determine, among patients who fail treatment with an initially assigned newer antipsychotic, the long-term effectiveness and tolerability of the newer atypical antipsychotics, relative to ziprasidone. We expect patients with weight gain, hyperglycemia, or hyperlipidemia will preferentially enter this Phase 2 trial. We hypothesize that treatment with ziprasidone will be associated with greater long-term effectiveness and tolerability than treatment with a newer atypical drug other than the one the patient initially received. Secondary analyses will contrast the two treatment groups in weight and metabolic measures.

Study Design

The Schizophrenia Trial will enroll 1,600 persons with schizophrenia (excluding first-episode and treatment-refractory patients).

Inclusion Criteria

1. Patients will be 18-65 years of age.

2. Patients must currently meet or have met in the past the DSM-IV criteria for schizophrenia.
3. Patients entering the study must, according to their own judgment in consultation with their physician, be appropriate for treatment with an oral medication.
4. Patients must demonstrate adequate decisional capacity to make a choice about participating in this research study and must provide informed consent to participate.

Exclusion Criteria

1. Patients with a DSM-IV diagnosis of schizoaffective disorder, mental retardation, pervasive developmental disorder, delirium, dementia, amnesia, or other cognitive disorders will be excluded.
2. Patients with well documented, drug-related, serious adverse reactions to even one of the proposed treatment arms will be excluded.
3. Patients in their first episode of schizophrenia will be excluded. Patients will be considered to be in their first episode if the patient first began antipsychotic drug treatment for psychosis within the previous 12 months and has had psychotic symptoms for less than 3 years.
4. Patients with well-documented histories of failure to respond to even one of the proposed treatment arms will be excluded. A treatment failure has occurred if the patient continued to demonstrate severe psychopathology in spite of fully adhering to treatment at an adequate dose of the medication for an appropriate length of time. Specific dose and duration criteria are as follows:

Olanzapine at dosages ≥ 30 mg/day for 6 consecutive weeks
Quetiapine at dosages ≥ 800 mg/day for 6 consecutive weeks
Perphenazine at dosages ≥ 32 mg/day for 6 consecutive weeks
Risperidone at dosages ≥ 6 mg/day for 6 consecutive weeks
Ziprasidone at dosages ≥ 160 mg/day for 6 consecutive weeks

5. Patients currently, or in the past, treated with clozapine for treatment resistance will be excluded. Patients who have taken clozapine for reasons other than treatment resistance may be eligible.

6. Patients currently stabilized on haloperidol decanoate or fluphenazine decanoate and who require long-acting injectable medication to maintain treatment adherent will be excluded.
7. Women who are pregnant or currently breast-feeding will be excluded. Women of child-bearing potential must agree to use appropriate contraception in order to enroll in this study.
8. Patients with tardive dyskinesia will be excluded from assignment to conventional antipsychotic treatment arms. (For the study definition of TD, please see The Tardive Dyskinesia Guidelines in Appendix B.)
9. Patients with a contraindication to any of the drugs to which they might be assigned will be excluded.
10. Patients with a medical condition that is serious and acutely unstable will be excluded.
11. Patients with the following cardiac conditions will be excluded:
 - Recent myocardial infarction (<6 months)
 - QTc prolongation (screening ECG with QTc > 450 msec for men, QTc > 470 msec for women)
 - History of congenital QTc prolongation
 - Sustained cardiac arrhythmia or history of sustained cardiac arrhythmia
 - Uncompensated congestive heart failure
 - Complete Left Bundle Branch Block (LBBB)
 - First-degree heart block with PR interval \geq .22 second
 - Concurrent treatment with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus.
12. Patients who have taken any investigational drug within 30 days of the Baseline Visit will be excluded.

PHASE 1

Patients will be randomly assigned to one of 5 treatment conditions for up to 18 months:

1. 300 begin double-blind treatment with perphenazine (PER)
2. 300 begin double-blind treatment with olanzapine (OLZ)
3. 300 begin double-blind treatment with quetiapine (QUET)
4. 300 begin double-blind treatment with risperidone (RIS)
5. 200 begin double-blind treatment with ziprasidone (ZIP)

PHASE 1a

Up to 200 patients screened and found to have TD who would otherwise be eligible for the study will be randomly assigned to one of the four atypical drugs in Phase 1a.

PHASE 1b

Patients who fail treatment with perphenazine will be randomly assigned to olanzapine, quetiapine, or ziprasidone in Phase 1b.

PHASE 2

Patients who discontinue their initial assigned treatment for any non-administrative reason will proceed to their second assigned treatment and will be followed for up to the remainder of their 18 month participation, as follows:

1. Patients originally assigned to one of the newer atypical antipsychotics who discontinue due to efficacy failure will be randomly assigned to double-blind treatment with one of the other two newer atypical antipsychotics which they had not previously received (50%) or with open label clozapine (50%).
2. Patients originally assigned to one of the newer atypical antipsychotics who discontinue due to tolerability failure will be randomly assigned to double blind treatment with one of the other newer atypical antipsychotics (OLZ, RIS, QUET) (50%), or with ziprasidone (if they had not previously received it) (50%).

PHASE 3

1. Patients who discontinue their Phase 2 treatment will be recommended open treatment based on their treatment history in the study. The treatment options include: clozapine, newer atypical antipsychotic (OLZ, RIS, QUET, ZIP, ARP), fluphenazine decanoate, and dual antipsychotic therapy (risperidone or perphenazine augmentation of current atypical drug).

Double-blinded Medications:

Olanzapine 5 mg	recommended dose range 5-20 mg/day
Perphenazine 8 mg	recommended dose range 8-32 mg/day
Risperidone 1.5 mg	recommended dose range 1.5-6 mg/day
Quetiapine 200mg	recommended dose range 200-800 mg/day
Ziprasidone 40mg	recommended dose range 40-160 mg/day

Primary Outcome Measure

Time to all-cause treatment failure marked by its discontinuation is the primary outcome variable. Although symptoms, side effects, functioning, costs, etc., are important outcomes, we chose treatment discontinuation as the primary outcome because it is a distinct and “sturdy” measure that reflects both efficacy and side effects and it is a clinically meaningful outcome. In the course of a patient’s treatment the need to change reflects the possibilities that the treatment was not sufficiently effective or tolerable, or the belief that another treatment would be superior.

There are basically six ways a drug will fail or will be discontinued:

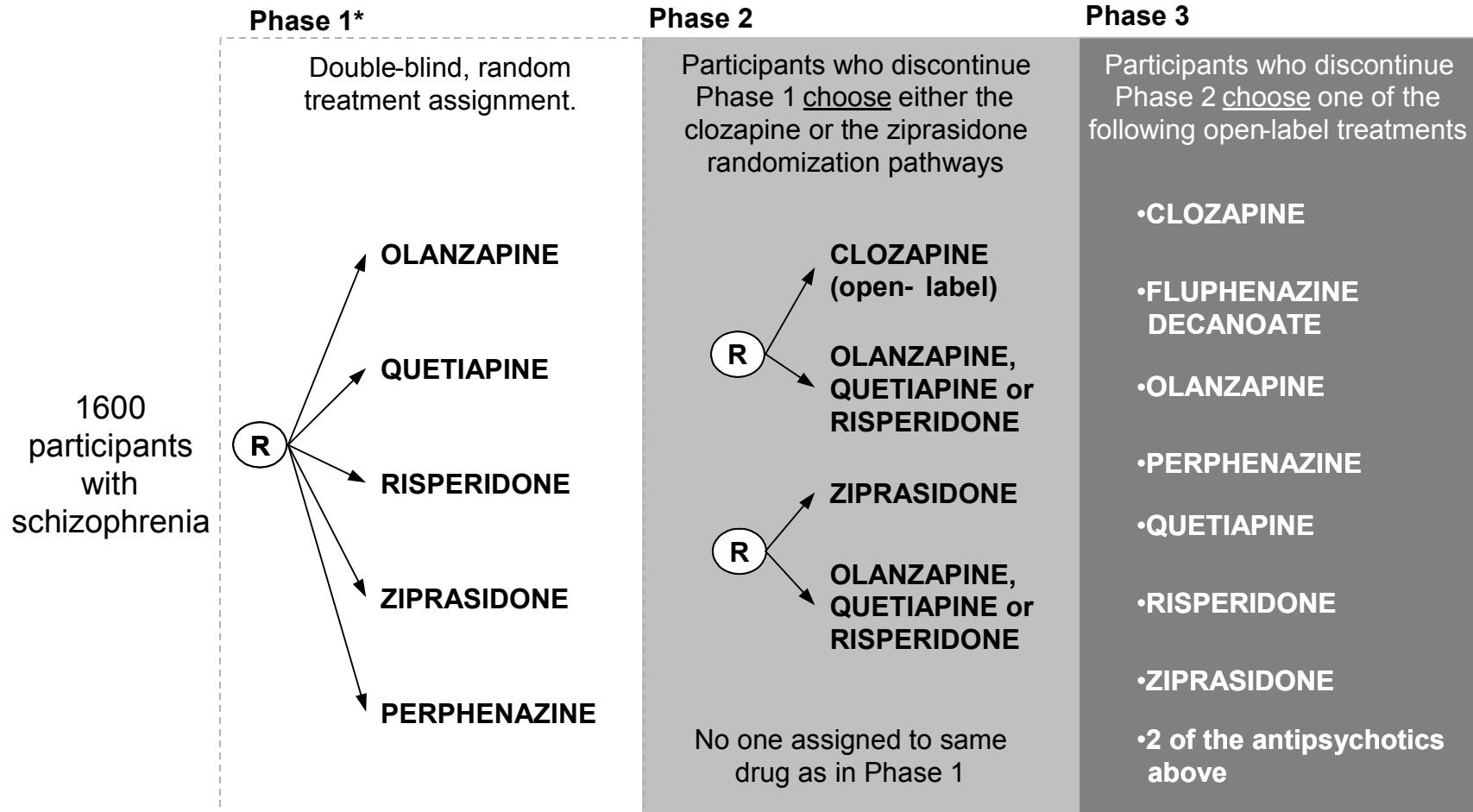
1. the clinician decides the drug is not useful
2. the clinician decides the drug is not tolerable
3. the patient decides the drug is not useful
4. the patient decides the drug is not tolerable
5. the patient does not want to take medication
6. the clinician and patient feel that there is another, superior treatment.

Guidelines will be provided to clinicians in the study to ensure that treatment changes are made only for logical and justifiable reasons, so that each treatment to which patients are assigned is given every chance to be effective before a switch is made. We will educate clinicians and patients so that they attempt to optimize dosing and the use of adjunctive medications before determining the drug is not useful, and so that they attempt to optimize dosing and the use of concomitant medications before determining the drug is not tolerable. Balancing this focus on participant retention, the safety and well-being of individual patients will be the primary considerations in all clinical decision making.

Secondary Outcome Measures

Additional assessments include measures for clinical and functional outcomes, safety, neurocognition, health service utilization and cost.

Schizophrenia Trial Design



Responders stay on assigned medication for duration of 18month treatment period

- * Phase 1A: participants with tardive dyskinesia (n=200) do not get randomized to perphenazine
- Phase 1B: participants who fail perphenazine will be randomized to an atypical (olanzapine, quetiapine, or risperidone) before they are eligible for Phase 2