The Risperidone Outcomes Study of Effectiveness (ROSE): A Model for Evaluating Treatment Strategies in Typical Psychiatric Practice

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We describe the design of a multicenter, randomized clinical trial to compare clinical, quality-of-life, and economic outcomes in patients with schizophrenia or schizoaffective disorder who were treated with risperidone or any of 13 conventional antipsychotic drugs approved for use in the United States. This 1-year trial was designed to approximate conditions of typical clinical practice: protocol-mandated care was minimized, and all health services (including medication) were provided according to usual community practices. Measures of interest included changes in psychiatric symptoms, medication side effects, health-related quality of life, satisfaction with drug therapy, therapy switching, rehospitalization for the management of relapse, the use of psychiatric services of all types, and the cost of psychiatric care. We review the rationale for this type of trial and discuss the potential value of such trials in setting policy and in clinical practice.

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Even with treatment, the course of schizophrenia is often marked by persistence of all or part of the spectrum of disease-related symptoms and by episodic exacerbation of symptoms and relapse. Relapse often results in hospitalization, disrupting the lives of patients and their families. Patients with a history of multiple admissions are at greater risk for subsequent rehospitalization.[1] Remission of symptoms and reduction in the rate of relapse are, therefore, among the primary goals of treatment.

The efficacy of antipsychotic drugs such as haloperidol and chlorpromazine in the treatment of schizophrenia is well established.[2] For a number of reasons, however, these agents fail to provide significant benefit to substantial numbers of patients.[3] The negative symptoms of schizophrenia (which are predictive of poor response) are often resistant to treatment with conventional antipsychotics,[4] and dopamine antagonists can themselves produce parkinsonian side effects that resemble these symptoms.[5] There are also a number of side effects associated with the use of conventional antipsychotics, particularly parkinsonian-like extrapyramidal symptoms (EPS)[6] and tardive dyskinesia, a potentially irreversible neurological side effect.[7] Many other factors, including the current mental health care system for schizophrenia, also contribute to inappropriate or inconsistent drug regimens.[8] Together, these and related circumstances often lead to the failure of current treatment to provide the desired benefit.

Risperidone is a serotonin 5-HT$_2$ receptor and dopamine D$_2$ receptor antagonist that was approved in December 1993 by the U.S. Food and Drug Administration (FDA) for use in the management of the manifestations of psychotic disorders. Results of clinical trials conducted to date suggest that risperidone is effective in treating both the positive and negative symptoms of schizophrenia.[9–11] The incidence of extrapyramidal side effects has been found to be low among patients receiving risperidone, and there is evidence that the risk of tardive dyskinesia may be reduced relative to conventional antipsychotics.[12] There is also preliminary suggestive evidence that disease-related cognitive impairment may be ameliorated with risperidone treatment relative to conventional agents.[13] Any increases in efficacy or tolerability associated with risperidone may result in an improvement in the disappointing outcomes of care associated with the use of conventional antipsychotics.

While the short-term efficacy of risperidone and conventional antipsychotics has been compared in several recent clinical trials,[10,13,14] there are no reports of longer-term

comparison of these agents. Furthermore, most studies of antipsychotics have evaluated their efficacy under controlled conditions of use. The use of defined treatment regimens in these studies, while maximizing the internal validity of comparisons of efficacy and safety, provides little information on the effects of typical patterns of antipsychotic therapy on key outcomes of psychiatric care (e.g., remission of symptoms, rate of relapse). The generalizability of results from these studies to conditions of typical psychiatric practice is therefore limited due to previously described characteristics of community drug treatment.[8]

We undertook a large, randomized effectiveness trial designed to address these issues. The design of this investigation is described below in detail. Results from the study will be reported elsewhere.

STUDY DESIGN

Overview

This study was a randomized, multicenter trial to compare the outcomes of psychiatric care over 1 year in patients with chronic schizophrenia and schizoaffective disorders who received initial therapy with risperidone versus a conventional antipsychotic agent. The study was designed to determine the impact of these alternative treatment strategies under conditions of customary clinical practice. Protocol-driven intervention was kept to a minimum, and patients obtained all medical care and pharmacy services through customary channels.

Outcomes of interest in this trial included changes in psychiatric symptoms, side effects, health-related quality of life, satisfaction with drug therapy and therapy switching, adverse events (whether drug-related or not), the use of psychiatric services and neuroleptic drug therapy, and the cost of psychiatric care. Information on the use of nonpsychiatric services and medications was not collected.

Investigator and Patient Recruitment

Physicians were recruited to participate in the study from a variety of treatment settings (e.g., Veterans Affairs, state, county, and private facilities) in order to maximize the generalizability of study results. Study centers were permitted to involve multiple clinics and providers as necessary to maintain ordinary therapeutic relationships for the treatment of the study participants. A total of 21 investigative sites in 17 states participated in the trial (Table 1). The study was approved by the institutional review board at each site.

Investigators identified and enrolled potentially eligible subjects among patients presenting for psychiatric care to their respective institutions. Patients were eligible to participate in the study if they were currently experiencing a relapse of schizophrenia, defined as an exacerbation of psychiatric symptoms accompanied by a change in the

Table 1. Regional Distribution of Study Centers for Risperidone Outcome Study of Effectiveness

Northeast/ Mid-Atlantic	South	Central	West
Connecticut	Georgia	Illinois	California
Maryland	Kentucky	Minnesota	Hawaii
Massachusetts[a]	Missouri	Ohio	Utah
New York[a]	North Carolina[a]	Oklahoma	
Pennsylvania[a]	Tennessee		

[a]2 sites.

level of utilization of psychiatric services. A complete list of study inclusion and exclusion criteria is presented in Table 2. Informed consent was obtained from each subject.

Sample-size estimation was based on an assumed 33% reduction in the rate of relapse requiring rehospitalzation over 1 year (23.5% and 35% for risperidone and conventional antipsychotics, respectively). The target level of enrollment was determined to be 656 patients (80% power with a type I error of .05 in a 2-tailed test), assuming a 20% loss to follow-up over a 1-year period. Enrollment was closed when a total of 684 patients were enrolled in the study across the 21 centers.

Interventions

Patients who met all study entry criteria and provided informed consent were randomly assigned to receive either risperidone or conventional antipsychotic therapy as initial therapy following relapse. Conventional therapy was defined as any of the 13 conventional antipsychotic drugs approved in 1994 by the FDA—chlorpromazine, chlorprothixene, fluphenazine, fluphenazine decanoate, haloperidol, haloperidol decanoate, loxapine, mesoridazine, molindone, perphenazine, thioridazine, thiothixene, or trifluoperazine—as selected by the treating provider. Oral, intramuscular, and depot formulations were permitted. Because the frequency of psychiatric hospitalization may be an important predictor of therapeutic outcome, patients were stratified prior to randomization according to whether they had had 1 versus 2 or more hospitalizations in the 2-year period prior to study entry.

Patients received all medications in a manner consistent with local standards of care. Thus, while at the beginning of the trial providers were encouraged to treat all patients according to their original treatment assignment (including those who relapsed), this aspect of treatment was not enforced, as the trial aimed to reflect the conditions of typical clinical practice. All decisions regarding medication changes (i.e., changes in dosage and frequency, as well as discontinuation or switching of therapy) were made solely at the discretion of treating providers. Patients were not randomly assigned to initial use of the only other atypical antipsychotic drug available during study enrollment (i.e., clozapine). However, subsequent use of all drugs was allowed.

Table 2. Trial Entry Criteria

A. Inclusion Criteria
   Eligible patients must:
   1. Be between 18 and 60 years of age at randomization
   2. Be currently experiencing a relapse of schizophrenia, defined as:
      A. Any admission (for 24 hours or more) to a psychiatric hospital or any admission to a nonpsychiatric hospital with a primary diagnosis of a mental disorder (ICD-9-CM diagnosis 290-319) within the previous 10 days
      or
      B. Any emergency room visit, contact with a crisis referral team, admission to a crisis bed, or unscheduled office or clinic visit
      and
      Exacerbation of symptoms of schizophrenia, confirmed by a Clinical Global Impression of at least 4 (moderately psychotic), and at least a moderate presentation of 2 of the following: delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness or persecution (patients who present with exacerbation of only 1 symptom may be enrolled on a case-by-case basis if the symptom is believed to be moderately severe)
   3. Have a diagnosis of the following chronic schizophrenia disorders, as defined by DSM-IV criteria: 295.1 (disorganized type), 295.3 (paranoid type), 295.6 (residual type), 295.7 (schizoaffective disorder), or 295.9 (undifferentiated type)
   4. Have had a diagnosis of schizophrenia before 35 years of age and at least a 2-year history of the disease
   5. Have had a history of at least 1 hospitalization or stay in a locked facility for chronic schizophrenia in the 2-year period prior to study entry
   6. Be in good general health as determined by history, physical examination, and laboratory testing (as necessary)
   Patients failing to meet all inclusion criteria were excluded from the study
B. Exclusion Criteria
   Eligible patients must not:
   1. Have a history of neuroleptic malignant syndrome
   2. Have a current diagnosis of bipolar disorder or catatonic-type schizophrenia, as defined by DSM-IV
   3. Have been continuously hospitalized for a psychiatric condition for more than 60 days within the 2 years prior to study entry
   4. Have a clinically significant abnormal laboratory or diagnostic test (as determined by the investigator) at baseline
   5. Have a history of medical conditions that would place the patients at significant risk by participating in the study
   6. Have used an investigational drug or participated in an investigational drug study within the 30 days prior to study entry
   7. Be pregnant or lactating
   8. Have a history of clozapine use, if the primary reason was minimal response to treatment with conventional antipsychotics
   9. Be at risk, in the investigator's opinion, of carrying out aggressive behavior that could endanger the life of another person
   10. Be at risk, in the investigator's opinion, of attempting suicide
   11. Have a history of previous failure of treatment with risperidone or of a serious adverse event or hypersensitivity reaction secondary to risperidone use

Providers were asked to discontinue all antipsychotic medications used prior to study enrollment within 3 weeks after randomization, unless their continued use was consistent with the assigned treatment. Again, this behavior was not enforced in order to permit the range of actual practice to be captured in the trial. The use of concurrent psychotropic medication was permitted at any time during the study. All psychiatric drug use was documented.

Patients obtained all medications through usual pharmaceutical sources. Payment was to be made by patients in their usual manner (e.g., cash, insurance program). Patients randomly assigned to risperidone who were financially unable to purchase the drug were informed about an existing, widely available program (Janssen Cares: The Risperdal® Patient Assistance Program) designed to help make risperidone available to those unable to purchase it through usual channels.

Follow-up

All patients randomly assigned to antipsychotic therapy were followed for 1 year regardless of treatment received. Study visits were scheduled at 4, 8, and 12 months following randomization for the purpose of collecting data on clinical outcomes. Patients who withdrew consent prior to study completion were asked to return for a termination visit.

Adverse Event Monitoring

Investigators were expected to report all adverse events occurring during the course of the study, regardless of their relation to study medication. All serious adverse events were followed until they were resolved or were determined by the investigator to be chronic and stable. Hospitalization due to reemergence of symptoms was considered a measure of treatment failure and was therefore not recorded as a serious adverse event.

Data Collection

Clinical outcomes. Complete psychiatric and medical histories were obtained, and a physical examination performed, at study entry. In addition, laboratory testing was performed as deemed clinically necessary to confirm patients as candidates for enrollment.

Psychiatric symptoms, side effects, health-related quality of life, and satisfaction with drug therapy were assessed at scheduled visits at baseline and again at 4, 8, and 12 months after study entry. Scales to assess these measures were selected on the basis of their applicability to the study population, clinical interpretability, and psychometric properties.

Symptoms of schizophrenia were assessed using 4 subscales derived from the 30-item Positive and Negative Syndrome Scale (PANSS)[15] as follows: positive symptoms,

Table 3. Measures of Symptoms, Side Effects, Satisfaction with Drug Therapy, and Health-Related Quality of Life

Symptoms
  Positive and negative syndrome scale
    Positive symptoms
    Negative symptoms
    General psychopathology
    Total
Side Effects
  Simpson-Angus Neurologic Rating Scale
    Total
  Barnes Rating Scale for Drug-Induced Akathisia
    Global
  Abnormal Involuntary Movement Scale
    Total
Satisfaction With Drug Therapy
  Drug Attitude Inventory (item scores)
    Item
Quality of Life
  Medical Outcomes Study 36-Item Short Form Health Survey
    Physical summary
    Mental summary
  Quality of Life Interview
    General life satisfaction

Table 4. Measures of Resource Use*

Resource	Measure
For the Management of Relapse	
Acute psychiatric hospitalization	Percentage of patients requiring rehospitalization
	Number of rehospitalizations
	Number of hospital days
Not Restricted to the Management of Relapse (Nonhospital Services)	
Partial hospitalization/acute residential treatment	Percentage of patients requiring nonhospital acute care services (ie, PH, ER, CT, CB)
Emergency room	Number of days patients received acute care services (ie, acute psychiatric hospitalization and non-hospital acute care)
Crisis team encounters	Number of visits for routine mental health services
Crisis bed use	Percentage of patients using selected other psychotropic medications
Routine mental health services (ie, psychiatrist, nonphysician medication and therapy, and case management)	
Use of study medications and selected other psychotropic medications (ie, anxiolytic or hypnotic agents, mood stabilizers, antidepressants, or anticholinergic agents)	

*Abbreviations: PH = Partial hospitalization/acute residential treatment, ER = emergency room, CT = crisis team encounters, CB = crisis bed use.

negative symptoms, general psychopathology, and total symptom score. Side effects were assessed using 3 scales: the 10-item Simpson-Angus Neurologic Rating Scale,[16] the 4-item Barnes Rating Scale for Drug-Induced Akathisia (BAS),[17] and the 12-item Abnormal Involuntary Movement Scale (AIMS).[18] Patient assessments for the PANSS, the Simpson-Angus Neurologic Rating Scale, the BAS, and the AIMS were made by the trained site investigator.

Both generic and disease-specific instruments were used to assess health-related quality of life. The interviewer version of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) was used to assess health-related quality of life in 8 separate domains[19]; attention was focused on 2 summary scales that describe physical and mental health.[20] The brief version of the Quality of Life Interview (QOLI)[21] was used to measure disease-specific quality of life in 9 subjective and 8 objective domains (Table 3); attention was focused on the general life satisfaction scale. Patients responded to the QOLI in a structured interview with a trained study coordinator. Patient satisfaction with drug therapy was assessed using the 10-item Drug Attitude Inventory (DAI)[22] (Table 3). Patients self-administered the DAI with the assistance of a trained study coordinator.

All relevant study personnel attended detailed training sessions on the proper administration of each of these instruments. Each site also received written and audiovisual training materials.

Health care utilization. Data were collected on the frequency and duration of acute psychiatric hospitalization for the management of relapse, use of nonhospital acute services (i.e., partial hospitalization or acute residential treatment, emergency room visits, encounters with crisis teams, use of crisis beds), visits for routine mental health services (i.e., psychiatrist, nonphysician medication and

therapy, and case management), and the use of other selected neuroleptic medications (Table 4). These data were directly obtained from medical records, pharmacy records, discharge summaries, or other primary sources of documentation collected by full-time study coordinators at the 21 sites. Coordinators were responsible for reviewing all records for all locations of care. Because it was not feasible to obtain primary cost information from all study centers, estimates of cost for each individual type of service measured in the trial were derived from secondary data sources.

Data Analysis Plan

An intent-to-treat perspective is planned for all primary analyses of data. The comparability of the 2 treatment groups at baseline will be evaluated with respect to clinical and demographic characteristics. Study measures will be compared between all patients randomly assigned to risperidone versus conventional antipsychotic therapy. In addition to the primary analyses of the intent-to-treat cohort, comparisons of subgroups are planned (e.g., by type of insurance coverage available to each patient).

Scale scores for psychiatric symptoms, side effects, health-related quality of life, and satisfaction with drug

therapy will be calculated at each time point. Changes in these measures over time will be assessed using linear mixed-effects models.

Measures of resource use (e.g., hospital days, routine mental health visits) will be summed for each type of service. Dollar values from secondary data sources will be assigned to the services to estimate costs for each type of service provided and for the total cost of psychiatric care.

Switches in antipsychotic therapy will be documented in 2 distinct ways. Switches across treatment arms, as well as switches outside either treatment arm (e.g., to clozapine) will be documented based on the investigator's assessment of treatment failure and requirements for changes in therapy. Changes in therapy within the conventional antipsychotic arm will be assessed using a computerized algorithm based on patterns of drug use observed during the period of follow-up.

A significance level of p ≤ .05 on a 2-tailed test will be used in all primary analyses of data. Because the trial is necessarily open-label, all study investigators involved in data analysis are blinded to treatment assignment; this blind will be maintained until the study database is locked for analysis.

DISCUSSION

The role of the traditional clinical trial is to identify agents that are efficacious and safe under optimal and controlled conditions. To fulfill this role, these trials typically use a double-blind design and attempt to control for confounding factors by means of narrow patient inclusion and exclusion criteria, strict treatment regimens, and enforced compliance with study therapy.

While a strength in some regards, these design characteristics mean that such trials often do not generalize to the real world of typical clinical practice. This is particularly the case with respect to antipsychotic and other neuroleptic agents. Many factors—including variability in dose titration, dosing form, and frequency of administration, insurance coverage and reimbursement, discontinuity of access to services, and noncompliance with prescribed therapy—may significantly affect the effectiveness of a drug in actual clinical practice. Protocol-influenced care provided in an efficacy trial may further limit the possibility of examining the impact of a drug on typical resource utilization and costs.

There is evidence that these issues may be of particular concern in treating patients with schizophrenia. Noncompliance with antipsychotic therapy is pervasive[23] and may lead to reemergence of symptoms and subsequent rehospitalization.[24] In addition, departures from optimal dosage and administration frequency are commonplace and may reduce the efficacy of a given drug.[25] For all of these reasons, the benefits observed in antipsychotic efficacy trials may not be indicative of the benefits that patients, provid-

ers, and health systems will obtain under the conditions of ordinary practice.

This study is intended to address many of these issues. It incorporates key components of experimental research (e.g., randomization) but goes beyond the realm of the traditional clinical trial by minimizing protocol-mandated intervention. In contrast to a traditional clinical trial, in which therapies are compared based on defined dosage levels and enforced compliance, our study randomly assigned patients to initial treatment *strategies* in which the dosage of medication, concurrent use of other drugs, changes in medication, and the frequency of follow-up encounters all were determined by local standards of care. Although investigators were encouraged to initiate treatment using the randomized intervention, there was no protocol direction of subsequent care.

The design of this study also permits examination of numerous factors that may influence the clinical and economic outcomes of drug therapy, including insurance status, number of prior hospitalizations, treatment setting at time of initial relapse, and therapy switching. These findings may help determine whether therapeutic failures are related to the drug selected or to other confounding factors that may not be readily apparent to the clinician. Furthermore, capture of information on resource use during the natural course of community care can provide more accurate assessments of the costs of therapies than pharmacoeconomic analyses that are included as components of traditional efficacy trials.

This type of pragmatic clinical trial has been conducted previously in a small number of therapeutic areas, including mental illness.[26,27] However, this is the first study of its kind among patients with chronic schizophrenia. Because the acquisition costs of newer antipsychotic drugs such as risperidone and their appropriateness for first-line use are being scrutinized by regulatory authorities, providers, and third-party payers alike, the questions explored by this study are relevant to the current health care environment.

Effectiveness trials can be seen as a gold standard in achieving the different but important aims outlined above. They have been advocated by governmental and advisory bodies for these purposes but remain little utilized. With the increasing pressure on health delivery systems to produce optimal outcomes at optimal cost, perhaps the time has come for evaluations of this type to be routinely considered to augment traditional efficacy evaluations.

Drug names: chlorpromazine (Thorazine and others), chlorprothixene (Tatactan), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), loxapine (Loxitane), mesoridazine (Serentil), molindone (Moban), perphenazine (Trilafon), risperidone (Risperdal), thioridazine (Mellaril and others), thiothixene (Navane), trifluoperazine (Stelazine).

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