Guest Editors’ Introduction:  
What Can Large Pragmatic Clinical Trials Do for Public Mental Health Care?  

by Jeffrey A. Lieberman and T. Scott Stroup

Persons in positions of responsibility often need to make important decisions with inadequate information. Those involved in public mental health care are no exception. Promising new treatments often come with high price tags, and decision makers must use whatever information they have to weigh benefits against costs. Of late, this tension has become more acute, threatening to reach crisis proportions. With the costs for health care once again rising at a rate that exceeds inflation and Federal and State governments facing budget shortfalls, increasing pressure is being placed on Medicare, Medicaid, the Veterans Health Administration, and private third party payers to limit expenditures (Abelson 2002; Freudenheim 2002; Pear 2002c). A growing number of people are uninsured, and the insured are expected to have fewer options and to face higher out-of-pocket expenditures (Strunk et al. 2001; Abelson 2002; Pear 2002a).

The revolution in biomedical research technology and the burgeoning knowledge base that this has produced, in concert with the prospect of large profits, have accelerated the pharmaceutical industry’s rate of drug development (Berndt 2001). Consequently, an increasing number of drugs are approved by the U.S. Food and Drug Administration (FDA) and introduced into clinical use each year (Berndt 2001). Antipsychotic drugs are a case in point. After the first antipsychotic drug chlorpromazine was introduced in the United States in 1953, 11 agents were approved by the FDA and made available for clinical use through 1989. Chlorpromazine was the prototype of a class of drugs that were initially termed neuroleptics but have since become known by a variety of names, including typical, conventional, or first generation antipsychotic drugs. In 1989, clozapine, considered the prototype of a second generation of antipsychotic drugs called atypical antipsychotic drugs, was approved by the FDA. In the 12 years prior to the introduction of clozapine, there were no new drugs approved as antipsychotics in the United States, while in the 12 years since clozapine, there have been six though only five are currently marketed for clinical use.

The newer drugs, still under patent protection, are priced many times higher than the older drugs, for which there are often generic versions. Because the new medications are promoted as having superior efficacy and/or safety, they are often used preferentially, thus increasing the costs of drug acquisition. Prescription drugs are the fastest-growing component of recent rises in health care costs (Levit et al. 2003). A result of this phenomenon is the proliferation of cost containment mechanisms—including preferred drug lists, treatment algorithms, prior approval procedures, and higher copayments—employed by third party payers (Berndt 2001). Despite their justification on economic grounds, such measures create concerns and conflicts among various stakeholders. Consumers and advocates want unrestricted access to the best available treatments, and they want to make sure that consumers of mental health care are not unfairly targeted by cost control efforts. Pharmaceutical companies want to be able to sell their products at market-based prices that will enable them to return a profit to their shareholders and fund their research and development programs. Mental health care clinicians want to be able to use the best treatments for their patients, and mental health care administrators want to provide high-quality care in a cost-effective manner.

How is one to effect a mental health care policy that satisfies all of these competing interests? If new treatments are indeed more effective, then the difference in their cost may be partially offset by reductions in the need for other services that patients receiving the treatments will require, as well as increased productivity. Indeed, this is the claim of the pharmaceutical companies and proponents of the new medications. However, the evidence for such claims comes largely from studies conducted as part of the phase III and IV development of the medications, along with optimistic extrapolations of these results. Objective and dispassionate analyses of the existing data provide neither a clear
nor a compelling picture of the comparative or cost effectiveness of the newer medications (Leucht et al. 1999; Geddes et al. 2000; Chakos et al. 2001; Wahlbeck et al. 2001; Sartorius et al. 2002; Tuunainen et al. 2002). Moreover, the data base available for such analyses is largely inadequate for deriving any definitive conclusions. If one searches the literature for comparative studies of second generation antipsychotic drugs that are randomized, are controlled, and have at least 30 patients per treatment group (minimal requirement for statistical power), only a small number of studies are to be found (table 1), and the majority of these are short-term acute treatment studies of efficacy and safety conducted by the various pharmaceutical companies in order to gain FDA approval and favorable product labeling. It is important to note that almost all of these studies excluded persons with comorbid conditions and severely restricted the use of adjunctive medications. Because these research designs are geared toward the regulatory requirements of the FDA, the results are difficult to generalize to the broader patient population and range of clinical settings and situations in which these drugs are used, particularly in public mental health care systems.

Thus, mental health care administrators and policy makers must make decisions about treatments and resource allocation with inadequate information. Indeed, a number of treatment practices prevalent in the public mental health sector have substantial cost implications for which there are wholly inadequate data. These include, in addition to the comparative effectiveness of antipsychotic medications, the effectiveness of multiple antipsychotics and adjunctive medications versus monotherapy, and the effectiveness of combined psychosocial therapies and pharmacotherapies. Where will conclusive data come from? How are consumers, clinicians, administrators, and policy makers to make informed choices?

In a bold, ambitious effort to address this critical need, the National Institute of Mental Health (NIMH) has launched an initiative in large pragmatic clinical trials targeting key questions in public mental health care. Other National Institutes of Health institutes have used such an approach for some time. Recently, similarly conceived trials have yielded interesting and in some cases surprising results that likely could only have come from such large and pragmatically designed studies (for example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT] study of antihypertensives and the Women’s Health Initiative Estrogen Plus Progestin Study [The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002; Writing Group for the Women’s Health Initiative Investigators 2002]).

The background to this NIMH initiative is the topic of the first article—by Lebowitz et al.—in this issue of the Schizophrenia Bulletin. It describes various aspects of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project, which is charged with determining the comparative effectiveness of antipsychotic drugs for conditions in which they are clinically indicated. The CATIE project is currently conducting trials in two mental disorders, schizophrenia and Alzheimer’s disease. The trials began in January and April 2001, respectively, and results are expected to be reported in the spring of 2005. Subsequently, the CATIE project intends to develop followup studies to examine other critical questions in the treatment of patients with severe mental illnesses requiring antipsychotic drugs.

This issue of the Schizophrenia Bulletin contains articles describing various aspects of the CATIE project and the perspectives of specific stakeholders. The articles by Stroup et al. (this issue) and Schneider et al. (this issue) describe the individual trials, which use hybrid designs involving many elements of efficacy and effectiveness studies (hence the term pragmatic clinical trials). The sample sizes are large and study durations are long in comparison to similar studies with these populations. In addition, there are multiple study stages that patients move through in an algorithmic fashion contingent on their clin-

![Table 1. Randomized controlled trials* of atypical antipsychotics with \( n \geq 30 \) per treatment group](http://schizophreniabulletin.oxfordjournals.org/)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of studies with conventional comparator</th>
<th>Number of studies with atypical comparator</th>
<th>Number of studies &gt; 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Clozapine</td>
<td>6</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Risperidone</td>
<td>12</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

* Studies with more than 1 of the above drugs are counted as individual studies for each drug. Thus, a study with clozapine and risperidone would be counted as 1 for clozapine and 1 for risperidone.
real responses to the initial and successive treatment assignments. Major emphases have been placed on evaluating patients on a broad range of outcomes, including psychopathology, safety and tolerability, adherence, cognition, comorbidity, service utilization, and cost. The measures and methodologies used in the trials are described in the articles by Swartz et al. (this issue), Keefe et al. (this issue), and Rosenheck et al. (this issue). Analyses of data from long-term studies with complex designs present special challenges. The article by Davis et al. (this issue) describes the statistical methods and data analysis plan for the CATIE project. The current usage patterns and access to new medications in the United States are illustrated in the article by Domino et al. (this issue), while the European perspective on the evidence for atypical antipsychotic drugs’ effectiveness is described in the article by Geddes (this issue). Among the most important stakeholders in this process are mental health administrators and consumers. Their perspectives on CATIE and what information is needed by the important constituencies that they represent are described in the articles by Ganju et al. (this issue) and Amador et al. (this issue). In designing the CATIE project, certain choices had to be made, given that no one study can answer all questions. The article by Essock et al. (this issue) provides a thoughtful discussion of study design alternatives and the relevant considerations in making decisions. Finally, the article by Smith (this issue) reminds us that even the most effective treatments have limitations that one must strive to overcome.

We are proud of this issue of the Schizophrenia Bulletin and appreciate the opportunity to discuss the CATIE project. We trust that future publications from the CATIE project will contribute importantly to the knowledge base on treatments for persons with mental illnesses and help consumers, clinicians, administrators, and policy makers better evaluate the available treatments and determine how best to use them.

References


Acknowledgments

This article was based on results from the Clinical Antipsychotic Trials of Intervention Effectiveness project, supported with Federal funds from the National Institute of Mental Health under contract NO1 MH90001. The aim of this project is to examine the comparative effectiveness of antipsychotic drugs in conditions for which their use is clinically indicated, including schizophrenia and Alzheimer's disease. The project was carried out by principal investigators from the University of North Carolina, Duke University, the University of Southern California, the University of Rochester, and Yale University in association with Quintiles, Inc.; the program staff of the Division of Interventions and Services Research of the NIMH; and investigators from 84 sites in the United States. AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Forest Pharmaceuticals, Inc., Janssen Pharmaceutica Products, L.P., Eli Lilly and Company, Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., and Zenith Goldline Pharmaceuticals, Inc., provided medications for the studies. This work was also supported by the Foundation of Hope of Raleigh, NC.

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