

## Introduction

# Evaluating the Evidence: Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Beyond

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Placebo-controlled efficacy trials conducted for U. S. Food and Drug Administration registration and approval purposes are an essential component of evidence-based pharmacotherapy. However, these *efficacy* studies have several shortcomings, including a very short duration (3–6 weeks) and rigid inclusion criteria that exclude subjects with a history of treatment resistance, coexisting medical illnesses, or comorbid substance use. Thus, the outcomes in real-world patients often fall short of the outcomes in controlled clinical trials. This “efficacy-effectiveness gap” necessitates that pragmatic trials of drug *effectiveness* be conducted in the real world to guide clinicians about the optimal use of pharmacologic agents. This gap is precisely why the landmark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was needed.

CATIE was supported by the National Institute of Mental Health with a seemingly simple goal of making a head-to-head comparison of the currently available atypical antipsychotics with the additional element of adding a conventional antipsychotic into the mix to compare the effectiveness of the old- and new-generation antipsychotics. The focus is not on efficacy but effectiveness, i.e., whether or not a drug works under the usual conditions of care.

Three other important elements in this study take it beyond traditional drug studies—setting, number of patients, and length. In general, studies conducted for approval of a

drug are directed toward determining safety and efficacy in a controlled clinical setting. These are usually placebo-controlled and short-term (a few weeks) and enroll a small, homogenous group of subjects. In contrast, CATIE phase 1 enrolled nearly 1460 patients, from a large number and variety of treatment settings, who participated for up to 18 months.

Helping practitioners interpret the results and utilize the wealth of information that this study provides is important. This special supplement begins with an overview of the CATIE results by this author. This overview describes the basic foundation and structure of the study and details some of the salient results. One of the important things to do with a landmark study of this proportion is to review it under the scrutiny of hindsight. No study is perfect in design or implementation, and we learn valuable lessons from this approach. As this article points out, “No one drug is perfect or preferred. Despite decades of intensive research, we are still left with imperfect choices.”

Peter J. Weiden, M.D., then reviews one of the major features of CATIE, which is effectiveness as determined by all-cause discontinuation. A prominent finding of the CATIE trial is the high (74%) all-cause discontinuation rate for all drugs.<sup>1</sup> Understanding the process and implications of this aspect of the study is crucial. This insightful review points out that, initially, a high discontinuation rate may be seen as a sign of failure of a drug, yet this process is considerably more complex. The decision to stay with, or change, antipsychotic medication may depend on multiple influences and considerations.

In the third article in the supplement, John W. Newcomer, M.D., reviews the evidence that, while antipsychotic drugs offer important benefits for many patients with severe psychiatric disorders, selecting the most appropriate antipsychotic treatment for individual patients depends on weighing the risks and benefits of any treatment against its potential adverse events. He details the impact of metabolic issues on this patient population and the current trends in managing these important health issues. Synthesizing the literature, including the results from the CATIE study, and delineating the health care impact on patients provide a valuable resource for clinicians.

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In the final article in the supplement, Jonathan M. Meyer, M.D., details the “real-world” lessons that we can learn from the CATIE study and points toward a future direction for the treatment of patients with schizophrenia and serious mental illness. Since this patient population has illness with a long-term, chronic course, clinicians need to consider treatment interventions in the context of a lifelong illness. Patients’ lives are multidimensional, and various elements need to be considered in addition to pharmacotherapy, such as psychosocial rehabilitation and a more continual awareness of a patient’s physical health.

The set of articles in this supplement underscores the lessons learned from the CATIE study and beyond. It pro-

vides clinicians with some new perspectives about treatment and offers substantial information to improve the quality of treatment and the quality of life for patients with serious mental illness.

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

#### REFERENCE

1. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209–1223