

Efficacy and Effectiveness of First- and Second-Generation Antipsychotics in Schizophrenia

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While efficacy as a concept is concerned with whether a treatment works under ideal conditions, effectiveness is concerned with whether a treatment works under the conditions of routine care. Large-scale clinical, pharmacy, and administrative databases can provide naturalistic data for effectiveness studies when appropriate methodology is employed. The Nathan Kline Institute Integrated Research Database includes patient-specific admission, demographic, diagnostic, medication, and discharge information from hospitals operated by the New York State Office of Mental Health. This database was used to study the effectiveness of first- versus second-generation antipsychotics in the treatment of schizophrenia and schizoaffective disorder. Switching off the index medication regimen prior to discharge (negative outcome) was our principal outcome of interest. We concluded that, as a class, second-generation antipsychotics were less likely than first-generation agents to be associated with premature discontinuation of an antipsychotic regimen, both when used as the initial medication regimen following hospitalization and as the second regimen following a prior medication switch.

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A revolution in the pharmacotherapy of psychotic illness began in 1952 with the introduction of chlorpromazine, the first antipsychotic agent. The development of other agents with similar pharmacologic characteristics followed, but for approximately 35 years the antipsychotic armamentarium remained relatively uniform. The first-generation antipsychotics (also known as neuroleptics, conventional antipsychotics, or typical antipsychotics) share a similar spectrum of action, appear to work principally through their blockade of the dopamine D₂ receptor,¹ and differ primarily according to their side effect profiles. First-generation antipsychotic agents have proved efficacious in reducing the positive symptoms of schizophrenia—hallucinations and delusions, for example—but the evidence for their efficacy in other outcomes is limited.² They also share a common propensity to cause motor side

effects, both acutely (tremors, dystonias) and chronically (tardive dyskinesia).

In 1989, a new antipsychotic, clozapine, was approved by the U.S. Food and Drug Administration (FDA) for the therapy of “treatment-resistant” schizophrenia. Clozapine was considered “atypical” because it did not cause the extrapyramidal side effects seen with all the first-generation antipsychotics. Clinical trials have demonstrated that clozapine has particular efficacy in treatment-resistant schizophrenia³ and in the prevention of suicide.⁴ However, the widespread use of clozapine has been limited by the risk of agranulocytosis and by its high side effect burden.

Beginning with the introduction of risperidone in 1994, a new wave of second-generation (or atypical) antipsychotics began to enter the therapeutic armamentarium. These medications aimed to replicate the advantages of clozapine, while maintaining more benign side effect profiles. Unlike clozapine, they were introduced as primary treatment agents, not specifically for the indication of treatment-resistant schizophrenia. Now that there exists a large and diverse array of treatment options with proven efficacy, the remaining questions for investigation are those of effectiveness.

EFFICACY AND EFFECTIVENESS

Efficacy as a concept is concerned with whether a treatment works at all, under ideal conditions. All drugs approved by the FDA must show efficacy in drug registra-

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tion trials, which is to say that they demonstrate the ability to control some symptoms better than placebo. In order to maximize the likelihood of correctly identifying a drug effect, studies of efficacy typically must test a homogeneous patient population, randomly assign patients to the active treatment or to placebo, and make detailed outcomes assessments.⁵

Effectiveness is concerned with whether a treatment works under the usual conditions of care. Patients who actually receive a medication in clinical practice may differ in many respects from the kinds of patients usually enrolled in clinical trials. For example, they may or may not be as motivated as patients in clinical trials, they may not meet the diagnostic criteria required for entry into a typical clinical trial, they may or may not have decisional capacity, or they may suffer from substantial comorbidities. Also, the alternative treatment against which a new treatment must be judged in practice is rarely a pharmacologically inactive treatment (i.e., placebo) but another, established medication. In order to identify drug effects under the conditions of routine clinical care, an effectiveness trial generally must involve a larger and more heterogeneous patient population than a drug registration trial, compare active treatments to one another rather than to placebo, and must yield information about clinically relevant outcomes. Effectiveness outcomes tend to be somewhat less detailed than the outcomes studied in smaller efficacy-oriented trials.

So-called “larger, simpler” trials represent an alternative to the smaller randomized efficacy trial and are more suited to the study of medication effectiveness. A current example of such a large-scale effectiveness study is the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project,⁶ which will include 1600 patients with schizophrenia at study centers across the United States. The goal of the study is to determine the relative effectiveness and tolerability of the second-generation antipsychotics relative to one another, to clozapine, and to a first-generation antipsychotic. Its primary outcome measure is time to all-cause treatment failure marked by discontinuation of the medication. (Because schizophrenia is a chronic illness, medication discontinuation is highly unlikely to represent clinical improvement, and is therefore a measure of negative outcome.)

Although such “larger, simpler” trials have some advantages, they suffer from certain limitations. First, in a study of such large size, only a small number of interventions can be studied, and, because of their expense, long time-horizon, and logistical complexity, only a few such trials can practically be run at any given time. Also, as with all experimental trials, the necessity of collecting informed consent from the subjects produces a sample selection bias, which may cause the subject population of the trial to differ from patients in usual clinical care. Such patient selection bias is of particular concern when the

target clinical population is one in which impaired decisional capacity (such as severe psychosis) is common.

NATURALISTIC DATA IN THE STUDY OF TREATMENT EFFECTIVENESS

The use of naturalistic data represents another potential method of studying medication effectiveness.⁷ The growing number of large-scale clinical and administrative databases produced by the ordinary, day-to-day operations of health care delivery systems makes such studies more feasible than ever before.⁸ Studies utilizing these naturalistic data are inclusive, examining whole patient populations undergoing routine clinical care. They are non-experimental and observational, following the outcomes of treatments actually prescribed during routine clinical care.

In conducting a study of naturalistic data, it is possible to simultaneously examine the outcomes of a large variety of actual treatment situations. The databases, in effect, compile tens of thousands of individual treatment decisions along with their outcomes. Researchers can ask complex questions of the data regarding the effects of medication sequence or conditional effectiveness (for example, “Which medication is most likely to be effective following a failed trial with the first treatment?”).

The principal disadvantage of studies using naturalistic data is the lack of random assignment to treatment. Patients have been assigned to treatments according to their symptoms and on the basis of a clinician’s judgment, rather than randomly, which may create a treatment selection bias. There is an ongoing debate as to how effectively such treatment selection bias can be overcome by statistical adjustment and experimental design considerations. Among the methods that have been proposed are matching patients according to relevant clinical characteristics (e.g., age, illness severity, treatment history), matching patients on the basis of their probability of receiving a given medication (propensity scoring), or performing post hoc statistical adjustment for covariates. Some authors contend that such adjustments can never be adequate, because it is impossible to determine all the relevant patient variables that may be confounded with treatment assignment⁹ and that only random assignment of treatments can overcome the possibilities of bias. Others have noted that, even when randomization is used, there is still the chance probability that patients may differ according to prognostically meaningful variables, and, as a consequence, even randomized trials often resort to statistical control.⁵ Despite the controversies regarding the adequacy of statistical controls in observational studies, at least 2 meta-analyses have demonstrated that, in practice, the results of well-designed observational studies do not systematically produce different assessments of treatment effect sizes than do randomized trials performed on the same topics.^{7,10}

Example: A Naturalistic Study of Antipsychotic Medication Effectiveness

This study utilizes a large-scale clinical database, the Nathan Kline Institute Integrated Research Database (NKI-IRDB) to compare the effectiveness of first-generation and second-generation antipsychotics (excluding clozapine) in a severely and persistently mentally ill inpatient population. The NKI-IRDB includes patient-specific admission, demographic, diagnostic, medication, and discharge information from hospitals operated by the New York State Office of Mental Health. The NKI-IRDB has been successfully used to examine the extent and pattern of use of depot neuroleptics, valproic acid, atypical antipsychotics, and combination antipsychotic therapies.¹¹⁻¹³ It has also been used to compare the outcomes of patients treated with risperidone to those treated with other antipsychotics.¹⁴

This study seeks to answer 2 questions. First, do first-generation or second-generation antipsychotics yield better outcomes when prescribed as the first medication regimen following hospital admission? Second, if a patient fails to respond to the first medication regimen, is a first- or second-generation agent the better choice for the second regimen?

Patients included in the analysis were all adult non-forensic patients admitted to Office of Mental Health facilities during the period 1996–2000, carrying a primary diagnosis of schizophrenia or schizoaffective disorder. We restricted our analysis to patients who received a single oral antipsychotic (monotherapy) as their first antipsychotic regimen. These inclusion criteria yielded a patient population of 7154 patients, 60% of whom were men and 57% of whom were diagnosed with schizophrenia (as opposed to schizoaffective disorder). Seventy-two percent of this population had at least 1 prior hospitalization in the state system since 1990 (mean number of hospitalizations = 1.76). On average, they had spent 268 days in a New York State hospital between January 1990 and their index admission. These findings suggest that this is a chronically ill group of patients.

The principal outcome assessed was a measure of medication ineffectiveness: the undesirable outcome of the patient's being switched, prior to discharge, off the initial antipsychotic regimen on to a different antipsychotic regimen within 180 days. (This is, in essence, a similar outcome to that used in the CATIE study.) The reason for this medication switch might be either inefficacy (lack of control of symptoms) or intolerance (e.g., due to high side effects).

Initial regimen. Patients who received, as their initial antipsychotic regimen following admission, oral monotherapy with a second-generation agent (risperidone, olanzapine, or quetiapine) were compared to those who received a single oral first-generation agent. Our analysis revealed that 28% of patients initiated on a second-generation agent

were switched off their regimen within 180 days. Among patients initiated on a first-generation antipsychotic, 44% were switched off. A multivariate logistic regression was used to adjust these outcomes for baseline differences in measures of illness severity (age at diagnosis, number of prior hospitalizations, and number of days spent in the hospital). The adjusted odds ratio for premature medication discontinuation (second-generation vs. first-generation) was 0.45 (significant, 95% confidence interval [CI]: 0.41 to 0.50).

Second regimen. Patients who failed on their first regimen and were not discharged were followed. We found that patients who were originally started on a *second-generation agent* and were then switched to a different second-generation agent had a 40% chance of being switched to a third regimen (bad outcome). Those who were switched from a second-generation agent to a *first-generation agent* had a 64% chance of being switched to a third regimen. The adjusted odds ratio for medication discontinuation (second-generation vs. first-generation) was 0.35 (significant, 95% CI: 0.24 to 0.53).

The patients who failed an initial regimen of a *first-generation agent* and were then switched to a second-generation agent had a 41% chance of needing a third trial. Patients who were switched from a first-generation agent to a different first-generation agent had a 60% chance of being switched to a third regimen. The adjusted odds ratio for premature medication discontinuation (second-generation vs. first-generation) was 0.45 (significant, 95% CI: 0.33 to 0.63).

Thus, patients receiving second-generation antipsychotics, as a class, were more likely than those receiving a first-generation agent to stay on their prescribed medication, both when it was prescribed as the first medication regimen following hospitalization and when prescribed as a second regimen following a switch.

CONCLUSION

Efficacy as a concept is concerned with the question of whether a treatment works at all, under ideal conditions, whereas effectiveness is concerned with the question of whether a treatment works under the usual conditions of care. With the increasing number and variety of antipsychotic medication choices, policy needs to be informed by effectiveness research. Naturalistic studies, such as those deriving from clinical databases, and larger, simpler trial designs can provide some useful answers to questions of drug effectiveness. Although the NKI-IRDB study examined the second-generation antipsychotics only as a class, testing effectiveness on a medication-by-medication basis will be important. Future studies are needed to determine whether there are notable differences in effectiveness among these second-generation agents.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others).

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