# New and old antipsychotics: what 'effectiveness' trials tell us

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## Abstract

Treatment options for patients with schizophrenia are more plentiful than ever before. Despite their established efficacy in treating schizophrenia symptoms, typical or first-generation compounds are associated with high rates of troubling extrapyramidal side effects. Moreover, there is still an unmet therapeutic need for the management of negative, cognitive and affective symptoms of schizophrenia. Second-generation antipsychotics were developed with the promise of enhanced efficacy and improved tolerability relative to their first-generation predecessors. The existing clinical trials, however, have not conclusively answered the questions about the clinical advantages and the cost-effectiveness of second-generation antipsychotics, especially from the perspective of clinical practice and public health. To address these issues, clinical trials of effectiveness have been conducted in the USA and the UK. Effectiveness trials are designed to answer the question 'Will a treatment work in real-world conditions?', whereas the existing industry-funded trials, often called efficacy trials, answer the question 'Will a treatment work under ideal conditions?'. Overall, effectiveness trials have shown that second-generation antipsychotics are as effective and cause fewer extrapyramidal side effects relative to first-generation drugs, but come with new metabolic side effects. A clinical advantage over all other antipsychotics was demonstrated for clozapine, the prototype of atypical antipsychotics. The goal for the next decade will be to use the current agents more intelligently, to match patients to drugs individually, and to continue the search for more efficacious antipsychotics and new add-on drugs for cognitive and negative symptoms.

**Keywords** antipsychotics; clozapine; first-generation antipsychotics; schizophrenia; second-generation antipsychotics

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## Introduction

Antipsychotic drugs have been the essential component of schizophrenia treatment for more than 50 years. Although all available agents have limitations in their effectiveness and are associated with various side effects, it is established that they improve schizophrenia symptoms and decrease relapse rates.[1–5]

The 'first-generation' (FGAs), 'typical', or 'conventional' antipsychotics were mostly high-affinity antagonists of dopamine $D_2$ receptors, most effective against psychotic symptoms but associated with high rates of troubling extrapyramidal side effects (EPSs) and tardive dyskinesia.[5] Negative symptoms respond beneficially to FGAs,[6,7] although FGAs may also contribute to 'secondary' negative symptoms in the context of EPSs, and act to obscure the gains of treatment. FGAs have been suggested to contribute to cognitive deficits of schizophrenia,[8,9] although more recent data have associated them with some beneficial effects.[10] FGAs have also been associated with worsening or induction of affective symptoms in the course of schizophrenia.[11]

By the early 1970s, the European experience with clozapine suggested fewer EPSs and greater efficacy relative to FGAs. Clozapine proved to have a clinical advantage over FGAs for positive and negative symptoms in patients with schizophrenia who had not responded to other antipsychotics[12,13] and also a potential beneficial effect on cognition[14] and affective symptoms.[15–17] However, clozapine's potential to cause agranulocytosis restricted its use to patients who had not responded to adequate trials of other antipsychotics.

The attempts to capture the enhanced therapeutic effect and reduced liability of clozapine to induce EPSs resulted in the development of second-generation (SGAs) or 'atypical' antipsychotics. Risperidone was one of the first widely used atypical agents, followed by olanzapine, quetiapine, ziprasidone, and aripiprazole. The question of whether SGAs have fulfilled the promise of enhanced efficacy relative to FGAs is a matter of ongoing research and debate; however, what is indisputable is that SGAs have become the drugs of choice for the pharmacological treatment of schizophrenia, supported by most standard treatment guidelines. However, meta-analyses of the relevant clinical trials have not provided consistent support for overall superiority of the SGAs,[18,19] although a relative superiority with regard to negative, cognitive, and mood symptoms has been supported.[19] SGAs cause fewer EPSs relative to FGAs,[20] and this acquires significance because EPSs are associated with noncompliance to treatment and can be disabling and stigmatizing

for patients. However, new problematic side effects, including severe weight gain, often accompanied by type 2 diabetes mellitus and hypercholesterolaemia,[21,22] have acted to attenuate the advantage of fewer EPSs. The question of whether SGAs represent a homogeneous group remains also unanswered. No conclusive differences were detected among amisulpride, risperidone, and olanzapine in a recent meta-analysis.[19] To complicate matters further, a recent report[23] analysed 42 industry-funded trials comparing atypical antipsychotics and found that different comparisons of the same two antipsychotic drugs led to contradictory conclusions, depending on the sponsor of the study.

Besides the relative clinical efficacy of antipsychotics, the cost-effectiveness of antipsychotic treatment becomes increasingly significant, as the more costly SGAs account for the majority of prescriptions.[24]

## Effectiveness trials

It would therefore appear that the existing clinical trials have not answered conclusively the questions about the clinical advantages and the cost-effectiveness of SGAs from the perspective of clinical practice and public health. To address these issues, the National Institute of Mental Health in the USA and the National Health Service in the UK separately funded effectiveness or 'pragmatic' clinical trials. These trials were designed explicitly to aid decision-making when faced with various choices concerning patient care.[25] The existing industry-funded trials, often called efficacy trials, answer the question 'Will a treatment work under ideal conditions?', whereas effectiveness trials are designed to answer the question 'Will a treatment work in real-world conditions?'.[26,27] Efficacy trials usually take place at specialized centres, use randomization, and employ relatively homogeneous samples by applying restrictive inclusive criteria; they usually use placebo as control, have intensive assessment strategies focusing on scales that measure the changes in psychopathology of the patients, and the duration of these studies is usually short. Creating optimal conditions, efficacy trials maximize sensitivity to detect desirable changes and are regarded as a necessary step in the development of new treatments in health care.[26] On the other hand, effectiveness trials usually take place at clinical practice settings and employ heterogeneous samples of usual patients, use usual dose ranges, and allow for dose titration, but have scientific rigour in that patients are usually randomized and raters are usually blind to assessment. Effectiveness trials gather information of maximum interest to clinicians and other decision-makers and use outcome measures that are clinically meaningful. These trials tend to use larger samples and have longer follow-up periods compared with efficacy trials. It should be stressed, however, that only after efficacy trials of a medication have demonstrated its ability to produce the desirable changes under optimal conditions is it worthwhile evaluating its effectiveness in real-world settings. In addition, because of the differences in design described above, there is usually a gap between efficacy and effectiveness of a pharmacological treatment. In other words, efficacy is necessary to, but not sufficient for, effectiveness.

### CATIE effectiveness trial

A total of 1493 patients with chronic schizophrenia participated in the US-based double-blind Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). Patients were randomly assigned to receive the FGA medium-potency drug perphenazine or one of the SGAs olanzapine, quetiapine, risperidone, and ziprasidone. Patients were followed for up to 18 months or until treatment was discontinued for any reason (phase 1). If the phase 1 treatment was perphenazine, patients who discontinued perphenazine were then randomly assigned to treatment with olanzapine, quetiapine, or risperidone (phase 1B). If patients in phase 1B again discontinued treatment, they then entered phase 2. In phase 2, patients could choose between two randomization pathways; the 'efficacy pathway' (phase 2E), recommended to individuals who discontinued the previous treatment as a result of inefficacy, compared open-label clozapine with double-blinded treatment with olanzapine, quetiapine, or risperidone, and the 'tolerability pathway' (phase 2T), recommended to individuals who discontinued the previous treatment as a result of intolerability, compared double-blinded treatment with olanzapine, quetiapine, or ziprasidone. Drug effectiveness was measured in this study with the time to all-cause discontinuation.

**Summary of phase 1 results**: rather unexpectedly, the results of CATIE phase 1 did not confirm the presumed superiority of SGAs relative to perphenazine. Instead, they indicated modest improvement for all patients over 18 months, but with no significant differences between perphenazine and any SGA as measured by psychopathology, quality of life, and side-effect measures.[28] In terms of time to all-cause discontinuation, olanzapine was associated with significantly longer duration of treatment relative to perphenazine (median of 9.2 months for olanzapine vs 5.6 months for perphenazine), whereas all the others were similar. However, olanzapine had the highest side-effect burden overall.

In addition, at the end of the 18-month follow-up period, three-quarters (74%) of all patients had discontinued the antipsychotic medication they started with, due to either lack of efficacy or tolerability, patient decision, or other reason. This finding suggests that discontinuation or switching of antipsychotic medication is the rule rather than the exception in the maintenance phase of schizophrenia treatment and that more often than not both patients and clinicians are not satisfied with the outcome of the treatment.

The neurocognitive effects of SGAs and perphenazine were also compared. The results indicated that the magnitude of cognitive performance improvement in patients with schizophrenia after 2 months of antipsychotic treatment was rather small, regardless of the class or type of medication employed. In addition, no significant differences between neurocognitive effects of the SGAs and perphenazine were found. Notably, perphenazine had the greatest effects on cognition after 18 months of treatment.[29] It would therefore appear that the improvement in cognitive performance in patients with schizophrenia still represents an unmet need of the pharmacological treatment of the disorder.

**Summary of phase 2 results**: non-responders to non-clozapine SGAs were the target group of this phase of the study, which investigated the benefits of switching to clozapine relative to switching to an SGA not previously received in the trial (olanzapine, risperidone, or quetiapine). Clozapine was superior to all three SGAs in terms of treatment discontinuation due to lack

 