Lessons to Take Home From CATIE

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The publicly funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) did not support superiority hypotheses for second-generation antipsychotic drugs in schizophrenia. Instead, the study supported the view that first- and second-generation antipsychotics have similar therapeutic properties and diverse adverse effect profiles. This emphasizes the importance of designing pharmacotherapy for the individual in order to optimize the benefit-to-risk profile. First- and second-generation antipsychotic drugs are extensively similar in mechanism of action, efficacy for psychosis, and lack of efficacy for avolition and impaired cognition. However, adverse effect profiles vary between drugs. The authors review the clinical implications of these data, with an emphasis on individualizing pharmacotherapy in an effort to reduce risk. Rather than selecting drugs on the basis of unfounded expectations of superior efficacy, clinicians can focus on selecting drugs and optimizing dosages to minimize adverse effects without sacrificing efficacy. Tardive dyskinesia may be a good reason to avoid a high dosage of first-generation antipsychotics, although the evidence for differential risk is less compelling for a modest dosage of low-affinity first-generation antipsychotics. Similarly, the metabolic effects of some second-generation antipsychotics can be decisive in considering risks. In either case, the clinician should detect earliest signs and take action while dyskinetic or metabolic effects are most reversible. Bottom line: the dichotomy between first- and second-generation antipsychotics was not supported by efficacy data (and now, is not supported effectiveness data). Only clozapine has documented superiority in treatment-resistant cases. (*Psychiatric Services* 59:523–525, 2008)

The most surprising thing about the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (1) is how surprised the field has been with the results. A common view has been that the second-generation antipsychotic drugs achieved the superiority of clozapine for positive symptoms, negative symptoms, and cognitive impairments, with a safety profile superior to clozapine and first-generation antipsychotics. Many studies sponsored by pharmaceutical companies have reported the advantages of the companies' second-generation antipsychotic, but little note has been taken of the fact that the Food and Drug Administration has not approved a superiority claim for any second-generation antipsychotic other than clozapine. In addition, little attention has been given to the failure of second-generation antipsychotics to demonstrate efficacy for primary negative symptoms (2,3) (the avolitional component of schizophrenia described by Kraepelin), and the reports of efficacy of second-generation antipsychotics for cognitive impairments have not separated true efficacy from other explanations, such as less adverse cognitive effects with a second-generation antipsychotic compared with a high dosage of haloperidol (4).

A more critical approach would note the following issues. First, the first- and second-generation antipsychotics share the same therapeutic mechanism of action initiated at the dopamine D_2 receptor. Second, serotonin antagonism has not been proven to enhance efficacy, although it may decrease adverse motor effects. The dopamine and serotonin antagonism mechanism is not essential for a drug to be classified as a second-generation antipsychotic (for example, amisulpride). Third, the mechanism for the superior efficacy of clozapine among treatment-resistant patients with schizophrenia is not established. Moreover, second-generation antipsychotics vary from each other substantially in their nondopamine pharmacological effects, which suggests that these additional actions do not account for class superiority.

There are few data to suggest that the efficacy of second-generation antipsychotics is superior to that of first-generation antipsychotics (5). Most of the data compare a second-generation antipsychotic to a first-generation antipsychotic, and haloperidol, at a substantial dosage, is the most common comparison drug in tests of second-generation compounds. When the data support superiority of second-generation antipsychotics, the differences are often very small and represent p value significance rather than clinical meaningfulness. Industry-sponsored studies provide most of the pre-CATIE data on comparisons between first- and second-generation antipsychotics, and analyses often

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used last observation carried forward, despite nonrandom differential attrition. In short, the data have not suggested substantial efficacy differences between these two classes of antipsychotics. Even when small advantages are observed, alternative explanations challenge superior efficacy reports. Finally, systematic meta-analytic studies done for the Cochrane Library (www.mrw.interscience.wiley.com/cochrane) routinely fail to document superiority claims. For a critical overview, which also considers adverse effects, see the article by Gardner and colleagues (6).

In short, in CATIE there was much reason to expect similar efficacy between the various second-generation antipsychotics and perphenazine (the first-generation antipsychotic comparison used in CATIE). There was also little reason to expect effectiveness differences between perphenazine and the second-generation drugs, because excessive dosing of the first-generation antipsychotic was avoided. In this context, CATIE, along with the United Kingdom's Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) (7,8), has made two major contributions. First, these studies have generated comparative data in head-to-head comparison of antipsychotics with funding support from public sources. Second, and perhaps most important, the results have stimulated the first influential debate on the pharmacotherapy of schizophrenia since second-generation antipsychotics swept the market.

Take-home messages

Clozapine has modest superiority over other antipsychotics for positive symptoms, which has been demonstrated in a number of designs, including those used in CATIE and CUtLASS. The failure of other second-generation antipsychotics to demonstrate this superiority should be taken very seriously. This suggests that poor responders to first- or second-generation antipsychotics are candidates for taking clozapine. The paradigm should be two steps, not three—that is, failure to respond to two antipsychotic drugs, then taking clozapine, rather than failure to respond to one or more first-generation antipsychotics and failure to respond to one or more second-generation antipsychotics, then taking clozapine.

Modest dosages of first-generation antipsychotics are likely to achieve maximum efficacy with minimal adverse effects. High dosages of first-generation antipsychotics are associated with dysphoria, sexual side effects, nonadherence, and increased risk of tardive dyskinesia.

In light of similar efficacy profiles, clinicians can select an antipsychotic according to which side effect profile is most benign for the individual. Because all antipsychotics have a similar mechanism of action and similar efficacy (other than clozapine), switching antipsychotic drugs is usually based on patient preference, adverse effects, or a switch to clozapine for an efficacy advantage. A second-generation antipsychotic should not be selected on the assumption that it has efficacy for primary negative symptoms or cognitive impairments. In CATIE perphenazine did ever so slightly better than the second-generation antipsychotics on the basis of neuropsychological measures, with the difference reaching significance in the 18 months of analysis (9). Second-generation antipsychotic studies have not met the clinical trial design requirements for testing efficacy for cognition (10) or negative symptoms (2).

Cost of treatment merits consideration at the individual treatment level as well as at the policy level (11).

Schizophrenia defines a high-risk population for cardiovascular disease, stroke, and diabetes. Patients with schizophrenia die about 26 years earlier than expected, and prevention of metabolic syndrome should be a treatment priority. All steps should be taken to avoid the development of this syndrome. Physicians should avoid prescribing a drug that is a substantial risk factor for metabolic syndrome in the absence of compelling evidence that benefits justify the risks. A plan to monitor weight and metabolic indicators and switch drugs if necessary is not satisfactory when the changes could have been prevented with another drug choice.

Clinicians should pay careful attention to adverse effects that complicate the clinical course. In comparison with higher dosages of haloperidol, some second-generation antipsychotics are generally associated with a better course of depression, less hostility, and perhaps less suicidality. The extent to which optimal dosing of first-generation antipsychotics addresses these issues and reduces the risk of developing tardive dyskinesia is not yet determined.

Strengths and limitations of CATIE

The strengths of CATIE are profound: a large and representative sample in real clinical settings with public sponsorship and head-to-head comparisons. In addition, careful attention was given to dosing. There is not sure knowledge as to how to level the playing field between antipsychotics when they are compared, but CATIE made an extensive effort to ensure that comparable dosages were used, although concerns have been raised about the quetiapine and ziprasidone dosages used in the study. The time on drug as the measure of effectiveness was also well considered, but any measure is vulnerable to criticism.

Many limitations can be noted and all studies have shortcomings. In our view, despite the various study limitations of CATIE, the results are consistent with a large body of literature using different designs, including CUtLASS, whose design was unique. We would like to emphasize two major issues in regard to the limitations of CATIE. First, the differential rate of dose titration may have made it more likely that olanzapine was optimally dosed. Second, patients randomly assigned to the drug that they were already taking at study onset tended to do better on the outcome criterion. This may simply suggest that drug response for that patient was established before the experimental phase. Because more patients were on olanzapine and risperidone at the time of random assignment, the design has a small bias in favor of these two drugs (12). We also speculate that if the study were conducted today, increased sensitivity to metabolic side effects would reduce the time-on-drug effectiveness measure for drugs with an adverse metabolic profile.

Conclusions

In summary, CATIE supports the view that first- and second-generation antipsychotics have similar therapeutic properties and diverse adverse effect profiles. This emphasizes the importance of designing pharmacotherapy for the individual in order to optimize the benefit-to-risk profile. Rather than selecting drugs on the basis of unfounded expectations of superior efficacy, clinicians can focus on selecting drugs and optimizing dosages to minimize adverse effects without sacrificing efficacy. Tardive dyskinesia may be a good reason to avoid high dosages of high-potency first-generation antipsychotics, although the evidence for differential risk is less compelling for modest dosages of low- or mid-potency first-generation antipsychotics (13). Similarly, the metabolic effects of some second-generation antipsychotics (but not all) can be decisive in considering risks. In either case, the clinician should detect earliest signs and take action while dyskinetic or metabolic effects are most reversible. Bottom line: the dichotomy between first- and second-generation antipsychotics is not supported by efficacy data (and now, effectiveness data), and only clozapine has documented superiority in treatment-resistant cases.

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