Effectiveness of antipsychotics

Is the CATIE trial a tsunami?

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Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353(12):1209-23.

Research question

Should we stop prescribing atypical antipsychotics and go back to first-generation medications?

Type of article and design

Randomized clinical trial

Relevance to family physicians

There has probably never been a psychiatric publication that has had as great an effect as the one published in September 2005 in the *New England Journal of Medicine* concerning the effectiveness of antipsychotics. Since family physicians often prescribe antipsychotics, this study has substantial implications for how they will prescribe such medications in the future. Discussion of results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study is important and of topical concern. As evidence, the number of commentaries published on this trial is amazing (36 listed on PubMed as of January 2006).

Overview of study and outcomes

The scientific community awaited the results with curiosity. The evidence that atypical antipsychotics have superior efficacy compared with conventional antipsychotics has been neither consistent nor robust.[1] The CATIE-Schizophrenia (CATIE-SZ) study was primarily aimed at comparing the effectiveness of first-generation antipsychotic (FGA) perphenazine versus second-generation antipsychotics (SGAs) ziprasidone, risperidone, olanzapine, or quetiapine. The index measure of treatment effectiveness was "any-/all-cause treatment discontinuation" over a period of 18 months. Discontinuation was not necessarily discontinuation to no medication, but from a double-blind situation to treatment with other antipsychotic compounds. The CATIE-SZ study aimed to reflect clinical practice, taking into account replacement or increase of dosage according to doctor-patient decision.

In the double-blind phase 1 (18 months), patients were randomized for treatment with FGAs or SGAs. Patients with tardive dyskinesia (TD) were enrolled in the study; however, because of safety and tolerance risks associated with FGAs, these patients were not assigned to the perphenazine arm of the study. For patients without TD, limited dosage of perphenazine was allowed to reduce extrapyramidal symptoms.

Results

It is noteworthy that patients with medical and psychiatric comorbidities participated in the study. The data showed that 74% of patients stopped treatment, with median time of 6 months. A quarter of the patients discontinued their antipsychotic treatment early due to inefficacy (24%, or 340 of 1432 patients), surpassed only by those discontinuing during phase 1 because of independent patient decisions to stop treatment (30%, or 428 of 1432). Time until treatment discontinuation for any cause was longer with olanzapine than with perphenazine, quetiapine, or risperidone. All prescribed medications were within their approved dose ranges except olanzapine, which was prescribed at doses as high as 30 mg daily. For details about the percentage of patients receiving the maximum dose at any time for each medication received see Lieberman et al. Hospitalization rates were significantly different within groups, but rates of treatment discontinuation due to intolerable adverse events differed between treatments and were non-significant after correction for multiple comparisons (lowest, risperidone, 10%; and highest, olanzapine, 18%). Moreover, more patients discontinued olanzapine because of weight gain—more weight than any other group—or metabolic effects (9% versus 1% to 4% with the other medications, $P<.001$), and more patients discontinued perphenazine because of extrapyramidal effects (8% versus 2% to 4%, $P=.002$). Thirty percent of patients receiving olanzapine gained more than 7% of their baseline body weight (average gain 1 kg monthly) compared with 7% to 16% of other groups ($P<.001$). Olanzapine was associated with significant changes in total cholesterol and triglycerides, and was temporally associated with greater increases in glucose and glucosylated hemoglobin A_{1c} relative to other agents. It should be mentioned that the ziprasidone group had improved metabolic variables, and that the risperidone group had increases in prolactin. It is crucial to note that 40% of the sample was obese at baseline, and that around 28% were also drug users.

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Analysis of methodology

Considering that industry sponsorship is a major factor in the reported superiority of one antipsychotic compared with another, the independence of this study's funding makes it highly credible. Unlike the majority of trials, which end after 6 to 8 weeks, this study lasted for 18 months. Furthermore, it compares SGAs with an FGA (phenothiazine) of the same family as chlorpromazine—the first neuroleptic prescribed—thus avoiding the usual comparisons with haloperidol, which tends to give more extrapyramidal symptoms when compared with SGAs. In addition, FGAs are not very different from atypicals (except olanzapine), which agrees with Jones' work conducted for the British government (227 randomized patients prescribed FGAs or SGAs).[2] The study confirms that olanzapine is more effective and has lower rates of discontinuation. Finally, the combined metabolic side effects and weight gain are of concern for olanzapine; this is not new, but warrants discussion of the risk-to-benefit ratio.

To answer our primary question, or to comment on whether such decisions can be made based on this study, remains difficult. No trial is perfect, and this one has several methodological problems. For example, although selecting patients randomized to perphenazine on the basis of lack of TD is ethically sound, a rather large group of patients with TD was allocated to the other treatments, and these patients are more likely to discontinue treatment or require treatment changes. Patients in this study were ill for an average of 12 years and were still at high risk of relapse. Many of them were married and nearly a third of the patients were not receiving any antipsychotic drugs at the time of the entry; thus, they were not representative of the average schizophrenia patient treated in Canada. Patients also had the option of moving on to the second stage of the trial after discontinuation. Investigators proposed dose ranges above those approved by the Food and Drug Administration. Lilly was the only pharmaceutical maker, however, that agreed to provide its product—olanzapine—at higher doses, as used in the study by Citrome and Volavka.[3] Meanwhile, quetiapine and ziprasidone were given below their optimal therapeutic doses. Although CATIE investigators acknowledged that dose differences could have been a factor influencing study results, this fact could be critically examined as a methodological problem. One of the major findings of the CATIE study is the extremely high rates of discontinuation of treatment. This requires a critical examination before being accepted as the norm for this population, and might be related more to the mental health system than to special patient characteristics of the population recruited.

Discussions are still very vivid among the diverse fan clubs of different medications. A meta-analysis by Geddes et al concluded that there is no evidence that SGAs are more effective and tolerated than FGAs.[4] In contrast, Davis et al concluded that some SGAs (olanzapine, risperidone, and amisulpride) are better than FGAs and should be prescribed as first-line treatment.[5] Both studies were based on changes in symptom scale scores. According to the Cochrane Group authors, perphenazine shows similar effects and adverse events when compared to other antipsychotics. They also show that incomplete and inconsistent reporting makes it difficult to draw clear conclusions about the efficacy of perphenazine.[6]

Application to clinical practice

In view of the CATIE findings, how long will it take family physicians, psychiatrists, and internists to change their practices to comply with a robust guideline such as that provided by the Canadian Psychiatric Association,[7] given that sufficient evidence of a regular follow-up of metabolic side effects is needed? As we pointed out a few years ago,[8] typicality is about dimension rather than category, and we suggested the use of the term "spectrum of atypicality." In this spectrum, family physicians, psychiatrists, and internists are destined to work together and to change together.

Bottom line

- In general, discontinuation rates were much higher than anticipated.
- Perphenazine is as efficacious as new antipsychotics.
- Olanzapine is superior on several variables but more deleterious metabolically.
- Weight and metabolic parameters were similar among perphenazine and SGAs, except for olanzapine.

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Competing interests

Dr Stip *has consulted for and received honoraria from Janssen-Ortho Inc, Lilly, and AstraZeneca. He has received grants from Lilly, AstraZeneca, and Novartis.*

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