Current PSYCHIATRY

Avoiding EPS is key to realizing 'atypical' benefits

CATIE finding is not unique to one antipsychotic class

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Many findings of the Clinical Antipsychotic Trials of Intervention Effectiveness in schizophrenia (CATIE) were unexpected,[1,2] but one was arguably the most surprising. It was that schizophrenia patients showed similar rates of extrapyramidal symptoms (EPS), whether treated with a first-generation antipsychotic (FGA) or any of four second-generation antipsychotics (SGAs).

This finding in CATIE phase 1 runs contrary to the understanding that SGAs, compared with FGAs, provide a broader spectrum of efficacy with significantly fewer motor side effects. A substantial body of evidence and virtually all schizophrenia treatment guidelines[3-5] support this prevailing view.

Did earlier schizophrenia treatment studies misinform us, or was CATIE's comparison of FGAs and SGAs "flawed"?[6,7] This article attempts to rec-

Table 1

5 key findings from CATIE phases 1 and 2

- **Olanzapine** was more effective than the four other antipsychotics (risperidone, quetiapine, ziprasidone, and perphenazine) in phase 1.[2]
- **Perphenazine**—a first-generation antipsychotic—was as effective as risperidone, quetiapine and ziprasidone in phase 1.[2]
- **Neurocognitive function** was no different whether patients were treated with perphenazine or SGAs, but adjunctive anticholinergic treatment worsened cognitive function.[8]
- **In phase 2,** clozapine was more effective than other SGAs in patients who discontinued phase 1 because of inadequate efficacy.[9]
- **Antipsychotics differed** in their adverse effect profiles, but no significant differences were observed between perphenazine and the SGAs in EPS rates or use of anticholinergic agents.[2]

oncile the divergent findings about antipsychotics and EPS and reveals a clinical pearl that suggests how to provide optimum antipsychotic therapy to schizophrenia patients.

WHAT DID CATIE FIND?

CATIE was a three-phase, 18-month, randomized controlled clinical trial designed to evaluate the effectiveness of five SGAs (risperidone, olanzapine, quetiapine, ziprasidone, and clozapine) and two FGAs (perphenazine and fluphenazine) in treating schizophrenia. Findings from phases 1 and 2 have been published or presented (*Table 1*),[2,8-9] and results from phase 3 are awaited.

CATIE phase 1 found no difference in efficacy, safety/tolerability, or effectiveness among perphenazine, risperidone, ziprasidone, and quetiapine. Soon-to-be-published data also will show no significant difference in cognitive effects among patients receiving perphenazine or any of four SGAs (risperidone, olanzapine, quetiapine, or ziprasidone).[8] Because no FGA was used in CATIE phase 2,[9-11] its results added little to phase 1 observations about how "typical" and "atypical" antipsychotics compare.

'Atypicals' and EPS. By definition, a reduced tendency to cause EPS (such as parkinsonism, dystonia, akathisia, and akinesia) distinguishes SGAs from FGAs. In fact, SGAs were called "atypical" because they disproved the belief that EPS are an unavoidable consequence of drugs that produce an antipsychotic effect.[12,13] The CATIE trial's inability to detect a difference in EPS rates between typical and atypical antipsychotics (*Table 2*)[2] is therefore the study's most surprising finding.

MAKING SENSE OF CATIE

Most studies suggest consistent differences between FGAs and SGAs in risk of EPS and tardive dyskinesia.[14-16] One explanation for CATIE's discrepant findings may be that the use of high-dose, high-potency haloperidol as the typical comparator in pre-CATIE studies magnified differences between FGAs and SGAs.[17,18]

Conversely, CATIE researchers minimized this difference by studying a population of schizophrenia patients at an unusually low risk for EPS. The study design:

- assigned 231 patients with a history of tardive dyskinesia to an SGA, without the opportunity to be randomly assigned to an FGA
- excluded patients with first-episode schizophrenia
- enrolled patients who had been treated with antipsychotics for an average of 14 years without a

history of significant adverse effects from study treatments.[19]

Just as prior studies might have exaggerated the EPS advantage for SGAs, CATIE might have minimized the FGA-SGA difference by studying a low-risk cohort in a way that reduced the trial's ability to detect such differences.

Interpretation. How can we reconcile the absence of a difference between FGAs and SGAs in EPS liability in CATIE with the preponderance of data suggesting otherwise? It appears that SGAs may be less likely to cause EPS than FGAs, but this difference is not evident in all populations. Furthermore, SGAs and FGAs differ in their ability to provide an adequate antipsychotic effect without EPS.

Among FGAs, low-potency agents are less likely to cause EPS or require concomitant anticholinergics than high-potency agents. Among SGAs, the gradient of EPS liability appears to be risperidone > olanzapine, aripiprazole, ziprasidone > quetiapine > clozapine (*Figure, page 44*). Clinically, these pharmacologic differences interact with physiologic differences in EPS vulnerability—some patients are more liable to develop EPS than others. Individuals who are more susceptible to developing EPS are more likely to benefit from antipsychotics with lower EPS liability.

CATIE found no difference among the various FGAs and SGAs with regard to overall efficacy, effects on cognition, and occurrence of tardive dyskinesia in treating chronic schizophrenia. Perhaps it was CATIE's failure to find a difference in EPS that explains its inability to demonstrate FGA-SGA differences in cognition and other effectiveness domains.

Table 2

CATIE: Similar EPS rates with perphenazine and SGAs*

EPS measurement	Perphenazine-treated patients	SGA-treated patients
Increased mean Simpson-Angus Scale score	6%	4% to 8%
Increased AIMS global severity score	17%	13% to 16%
Increased Barnes Akathisia Rating Scale score	7%	5% to 9%
Anticholinergic added	10%	3% to 9%

* Differences were not statistically significant
EPS: extrapyramidal side effects
SGA: second-generation antipsychotic
AIMS: Abnormal Involuntary Movement Scale

Source: Reference 2

WHAT CATIE TELLS US

The exaggerated view of SGAs as uniformly more efficacious, safer, and better tolerated than FGAs needs to be revised. At the same time, however, the results of CATIE should not be over-interpreted. They tell us that if the four phase 1 SGAs and the FGA perphenazine are used at certain dosages in a particular manner in a specific schizophrenia population—chronic, moderately ill, without tardive dyskinesia—then no differences might be expected among these antipsychotics. But CATIE's findings might not generalize beyond individuals with schizophrenia at low risk for EPS.

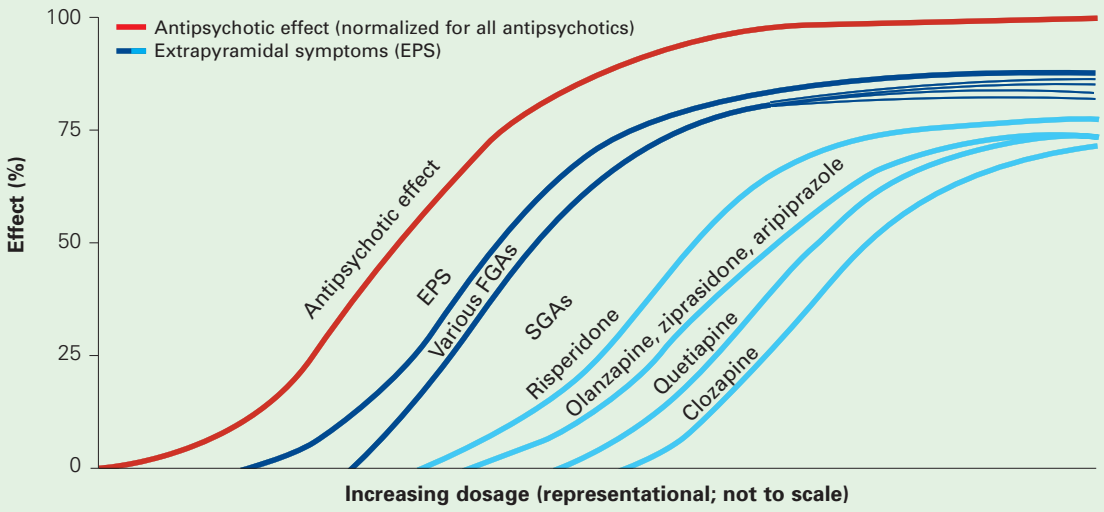
CATIE underlines the importance of achieving an adequate antipsychotic effect without EPS and without using anticholinergics. Clinical consequences of EPS extend beyond motor manifestations and include:

- worse cognition (*bradyphrenia*)
- worse negative symptoms (*neuroleptic-induced deficit syndrome*)

continued

Figure

Dose-response curves: Antipsychotic vs extrapyramidal effects



All FGAs and SGAs produce an equivalent antipsychotic effect (red), but they vary in the degree of separation between dosages at which their antipsychotic and extrapyramidal effects occur.
Source: Adapted from reference 13

- worse depression and suicidality (*neuroleptic dysphoria*)
- higher risk of tardive dyskinesia.[20]

SGAs' presumed ability to provide broader efficacy—cognition, negative symptoms, dysphoria—and lower risk of tardive dyskinesia appears to be driven by their lower EPS liability in association with an equivalent antipsychotic effect. Evidence for an SGA advantage independent of this effect is weak.[21,22]

Thus, CATIE's inability to find an FGA-SGA difference in EPS might explain its failure to observe an FGA-SGA difference in cognition and other effectiveness domains.

THE CLINICAL PEARL

Avoiding EPS and anticholinergics appears to be the key to improving cognition, dysphoria, and negative symptoms with FGAs *and* SGAs. SGAs' ability to achieve an equivalent antipsychotic effect without EPS also seems related to their lower risk of tardive dyskinesia.

SGAs' main advantage may be their greater ease of achieving an adequate antipsychotic effect without EPS or the need to add an anticholinergic to treat or prevent EPS. This comes from the broader separation between dosages at which SGAs produce their antipsychotic versus EPS effects, compared with FGAs (*Figure*).[13]

In clinical practice, then, we must achieve an adequate antipsychotic effect for our patients without EPS—whether we are using FGAs or SGAs—to obtain "atypical" benefits. The purported benefits of an "atypical" antipsychotic are not unique to a particular class of agents but relate to achieving a good antipsychotic effect without EPS—and the SGAs are better able to accomplish this than the FGAs.

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Table 3

Treating chronic schizophrenia: 4 clinical tips from CATIE

Minimizing extrapyramidal symptoms (EPS) is essential, whether using FGAs or SGAs
Avoiding EPS and not using adjunctive anticholinergics is the key to SGAs' purported benefits, such better cognition, less dysphoria, lower negative symptom burden, and lower risk of tardive dyskinesia
Antipsychotic dosing is key to accomplishing an adequate antipsychotic effect without EPS
Match the antipsychotic choice and dosage to the individual patient's vulnerability, then make adjustments based on response

Careful EPS monitoring is crucial to achieving optimal antipsychotic therapy. Reduced emphasis on EPS in the past decade (in awareness of EPS and training to detect symptoms) and overlap between behavioral aspects of EPS and psychopathology need to be addressed.

CATIE confirms clinical observations that:

- no antipsychotic is always superior
- schizophrenia therapy must be individualized.[23,24]

Different agents are associated with different adverse effects, which can make achieving maximum efficacy and safety/tolerability challenging. But differences among antipsychotics and heterogeneity in individual response and vulnerabilities may allow us to optimize treatment.

Different agents at different dosages may provide the best outcomes for individual patients, and the optimal agent and/or dosage can vary in the same patient at different stages of the illness. The CATIE trial contributes to evidence that guides our efforts to provide optimal antipsychotic treatment of schizophrenia (*Table 3*). Its "surprising" findings are most useful when considered in the context of the database to which it adds.[25]

Bottom Line

When treating a schizophrenia patient, strive for an adequate antipsychotic effect without EPS or having to use an anticholinergic. Consider his or her vulnerability for EPS, weigh each antipsychotic agent's liability to cause EPS, and give appropriate dosing.

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Related resources

- Tandon R. Comparative effectiveness of antipsychotics in the treatment of schizophrenia: What does CATIE tell us? Parts 1 and 2. *Int Drug Ther Newsl* 2006;41:51-8;67-74.
- Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study. www.catie.unc.edu/schizophrenia.

DRUG BRAND NAMES

Clozapine • Clozaril
Fluphenazine • Permitil
Olanzapine • Zyprexa
Perphenazine • Trilafon
Risperidone • Risperdal
Quetiapine • Seroquel
Ziprasidone • Geodon

DISCLOSURES

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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