What CATIE Did: Some Thoughts on Implications Deep and Wide

David Cunningham Owens, M.D., F.R.C.Psych.

The author discusses five lessons that can be learned from the seminal results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The lessons extend beyond practice implications to fundamental questions about how psychopharmacology studies are conducted and how results are interpreted and given relevance in regard to prescribing. The author recounts the history of the term "atypical" and how it came to be understood in the context of antipsychotics. The error of using high-dose haloperidol as a comparator in assessments of new antipsychotics—and of generalizing from the results of these studies—is also discussed. The CATIE results force uncomfortable questions about the extent of knowledge concerning the clinical pharmacology of a major treatment modality, which the author illustrates by examining possible reasons for the differential clinical actions of clozapine. The author concludes that CATIE benefited both patients and clinicians by opening up to patients the full gamut of antipsychotics for treatment planning and by reinstating to physicians their key skill in expert, individualized prescribing. (*Psychiatric Services* 59: 530–533, 2008)

Human affairs rarely progress in straight lines. Sudden jolts—pivotal events—can shake the surest orthodoxy. It could be argued that the first publication in September 2005 from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (1) was a pivotal event for psychiatry, for rarely within our profession has a surer orthodoxy been so comprehensively shaken. CATIE's "bottom line" has met with various reactions, outside the United States as much as within (2–4), but disregard—especially "sniffy" disregard—is not an option, even if the lessons are hard. CATIE offers many lessons that, if we take its findings as indeed pivotal, go beyond national practice recommendations and cut deep to the heart of psychopharmacology.

Lesson 1: R.I.P. "atypical"

The history of "atypical" as applied to antipsychotics should have urged caution because it is not a happy one (5). The term was generically applied in the 1970s to "Castor and Pollux" drugs that, like the twins of mythology, possessed dual attributes—in this case, effectiveness against negative symptoms as well as positive symptoms and diminished likelihood of causing extrapyramidal side effects. Such lofty expectations could not be fulfilled, and first pimozide, then thioridazine, and then sulpiride rejoined the pack.

In the second incarnation of "atypical antipsychotic," many pharmacological properties have been proposed to define it, but no single property has received universal acclamation (6,7). Thus "atypicality" continues to rest on a clinical characteristic—reduced liability to promote parkinsonism (5). This is fraught territory, because antipsychotic-induced parkinsonism is a poorly studied, perverse phenomenon (5,8). The idea that we had "two dichotomous groups" of antipsychotics (9), one "new" and the other merely "conventional," always had for many an aspirational feel, and some did urge caution (10). However, even alternative terms, such as "new generation" or "second generation," may actually have added to the idea that what was "new" must indeed be different, because it still justified subclassification. Caution, however, could not withstand the emotional appeal of the new and the power of promotional budgets, an unstoppable combination. If CATIE and other studies that support its findings (11,12) teach us anything, it is that "new" in relation to antipsychotics means simply "launched more recently"; that if enhanced tolerability is the advantage attributed to a new drug, you had better choose a robust side effect to validate the claim; and that "atypical" is an overvalued idea!

A generation of psychiatrists has trained in virtual ignorance of what came before "atypical," and a generation of patients has grown up overinfluenced by the power of marketing. Reestablishing the prescribing balance that CATIE demands will not be easy, but a good start would be—for the second time—to retire "atypical" from our vocabulary and our thinking. It has been much abused and could do with a rest.

Dr. Owens is professor of clinical psychiatry, Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Morningside Terrace, Edinburgh, Scotland EH10 5HF (e-mail: david.owens@ed.ac.uk). *This commentary is part of a special section on the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and its implications. Marvin S. Swartz, M.D., served as guest editor of the special section.*

Lesson 2: "Common" practice is not the same as "good" practice

The universal acceptance of haloperidol as the standard comparator in appraisals of new agents was unfortunate, even though it reflected "common practice"—specifically U.S. practice (5). By its 30th birthday in 1988, haloperidol was the market leader in sales terms, with a reputation as "easy to use." It is certainly rather difficult to kill someone with haloperidol, so technically it does have a wide therapeutic index. However, replace the word "safety" in the therapeutic index with the word "tolerability" and a different picture, of a rather difficult drug to use, emerges. Rosenheck (13) has provided an elegant, literature-based exposition of the use of haloperidol as a comparator. It is a high-potency, relatively D_2-selective compound with a high—possibly uniquely high—propensity to induce extrapyramidal side effects (8), yet it was chosen as the baseline for compounds of generally lower potency that have broad receptor-binding profiles and are postulated to have lower liability for promoting extrapyramidal side effects! In retrospect, this seems a bit of a "no contest" and should have seemed so at the time.

More to the point were the doses. The proclivity of U.S. psychiatrists for prescribing high-dose–high-potency antipsychotic regimens was known by the late 1980s (14), a practice that resulted in doses on average 3.5 times as high as equivalent ones for patients receiving low-potency drugs (15). These were the days before treatment guidelines; however, the facts were known when the efficacy studies for new drugs were being considered, as was the implication that such regimens would produce more extrapyramidal side effects. The lore of "common practice" seems to have blinded us to this tendency to overtreatment in the efficacy studies for new antipsychotics, all of which used haloperidol doses considerably higher than the minimum effective ones (5).

One lesson for the future is that the choice of comparator for assessing new antipsychotics should give at least a nod to pharmacological comparability. But the primary lesson is that comparator doses must reflect "good" as opposed to "common" practice.

Lesson 3: Generalization is a sin

Considering haloperidol's profile and limitations as a "representative" antipsychotic, there should perhaps have been greater circumspection in interpreting comparative data—that is, advantages of new agents over haloperidol may not have meant advantages over all available compounds. Generalization is a rhetorical device favored by politicians and others wishing to sway audiences when supportive facts are flimsy. As logicians will testify, however, it violates the rules of logic. So-called "conventional" antipsychotics are pharmacologically diverse, which is reflected in their highly variable tolerability, particularly neurological. When tolerability is promoted as the characteristic of difference, no single compound can be considered representative. In the future, claims for new drugs should be restricted to where the evidence, not where the marketing money, leads.

The prize for any drug (and its manufacturer) lies in a favorable perception of its role in the treatment of its target condition—that is, its place within the "pecking order" of options, which is an indicator of potential market share. On the basis of the initial efficacy studies, new antipsychotics were rapidly propelled to prominence, a mind-set reinforced among clinicians by treatment guidelines. In the future it would be premature to determine "place in treatment" on the basis of efficacy alone, especially when industry-sponsored studies are the sole or predominant source of the data. The distinction between efficacy and effectiveness has been clear for two decades, a distinction whose importance is affirmed by CATIE and its trans-Atlantic cousin CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Severe Schizophrenia) (12). For future drugs, advocates of guidelines might best fulfill their stated aim of quality improvement by exercising restraint with recommendations until the broader picture comprising both efficacy and effectiveness emerges.

Lesson 4 : Do we understand the clinical pharmacology of antipsychotics?

This lesson is in the form of a question. However, the question raises so many questions in itself that it is perhaps the most important lesson of all. Could it be argued that our present pickle reflects a fundamentally blinkered understanding of the clinical actions of antipsychotics? Perhaps an argument can be outlined by using clozapine as an example.

Not even I—a pre-CATIE skeptic—would claim that clozapine is "one of the pack." But what is the nature of its difference? The U.S. multicenter clozapine study of treatment-resistant schizophrenia (16) suggested three possibilities that might explain its undoubted advantage.

The first possibility is clozapine's enhanced extrapyramidal tolerability. An obvious test of "atypicality," which is surprisingly infrequently used, would be among patients with idiopathic extrapyramidal disease, such as patients with Parkinson's disease, who develop psychotic symptomatology. Such patients are notoriously difficult to manage because of inherent sensitivity to extrapyramidal side effects. In high-quality randomized controlled trial (including non–industry-sponsored trials), only clozapine was shown to improve psychotic symptomatology among patients with Parkinson's disease without exacerbating motor disorder (17,18). On this tolerability parameter, clozapine is unique within its class and therefore clearly different.

A second possibility is clozapine's efficacy in treating negative symptoms. Clozapine improves negative states (16), whereas convincing evidence for other pharmacological interventions remains weak (19). Clozapine's effect is conventionally interpreted as efficacy. But is it? This is a confusing area for therapeutic evaluation, which is complicated by an unintended consequence of Crow's type 1/type 2 hypothesis. Crow (20) suggested that the negative symptoms of schizophrenia, unlike positive symptoms, were associated with structural change in the brain and thus would be unlikely to respond to antipsychotic drugs. This hypothesis stimulated

vigorous debate (21) and became the most influential source of hypothesis-testable research throughout the 1980s, spawning a vast literature. However, for testing, the hypothesis demanded conversion of "negativity" in schizophrenia from the traditional view of something affecting higher domains of (psychosocial) functioning assessed longitudinally into something that was symptom led and assessable by cross-sectional evaluation (5). It is doubtful whether the varied manifestations of "negativity" (22) can be validly delineated via cross-sectional clinical assessment alone; a particular problem is the subjective component of drug-induced bradykinesia, a pervasive effect whose boundaries remain unclear (8).

So why is it universally assumed that benefits shown by a drug in treating negative symptoms reflect efficacy rather than, as in clozapine's case, the far more likely possibility that this is another manifestation of favorable neurological tolerability? Indeed, if negative symptoms rated on scales for negative symptomatology are found among normal volunteers who are taking antipsychotics that are prone to produce extrapyramidal side effects (23,24), why is this not the automatic assumption? Antipsychotics promote complex, subjective "negative" phenomena. These phenomena remain poorly delineated, but their resolution in "treatment" contexts surely sits more comfortably under the rubric of tolerability than efficacy.

The third possible explanation of clozapine's advantage is an enhanced efficacy on positive symptoms.

In the multicenter clozapine study, participants who received clozapine experienced significant overall reduction in total scores on the Positive and Negative Syndrome Scale compared with those who received chlorpromazine plus benztropine (16), although the enthusiasm this finding generated was perhaps greater than these modest advantages justified. Clozapine immediately became the sole antipsychotic with "enhanced efficacy." Once again, in our post-CATIE climate of questioning, we must ask whether this is correct. There is a curiously disregarded literature pointing to increasing doses of antipsychotics triggering the law of diminishing returns (5)—something long attributed to increasing neurological complications (8,25). Again, one must ask why this fact figures little in interpretations of clozapine's actions on positive symptoms. Why is the obvious explanation not simply that patients' positive symptoms decrease when the dysphoric "arousal" underlying drug-induced extrapyramidal dysfunction is reduced (13)?

Semantics, you may say! Improvement is improvement no matter how it is mediated. Putting aside the fact that this is hardly clinically rigorous, far less scientifically rigorous, CATIE represents such a "pivotal event" that everything is—should be—on the table for debate. Another lesson, which was there to be learned long before CATIE, is that conceptualization matters and that psychiatry is conceptually sloppy!

Lesson 5: A new "golden age" beckons

This may all seem a bit depressing. Far from it—CATIE is liberating! Having returned to the notion of a single class of drugs, clinicians can open practice to the full gamut of antipsychotic options, introducing truly "tailored" prescribing in which extrapyramidal side effects are no longer a uniquely frightening bogeyman but only one of a number of bogeymen to be confronted. One model comes from drug regulation, in which product licenses are granted on a "risk-benefit appraisal," where the "added extra" is clinical expertise (5). There are now a range of variables we can enter into our individualized risk-benefit prescribing appraisal: age; weight or fat distribution; metabolic parameters; past or present status in regard to extrapyramidal side effects; individual history of diabetes, hypertension, or other cardiovascular risks; family history of these conditions; level of treatment engagement; adherence history; and so forth. If a key psychiatric skill is expertise-based prescribing, we now have the opportunity to reestablish our credentials, which of late have been universally undervalued.

And the next time we attend an "educational" meeting in a sunny location, we, as clinicians, need not feel intimidated by the platform expounding the merits of this compound or that on the basis of in vitro binding or some other erudite laboratory parameter. Thanks to CATIE, we can point out with confidence that the ultimate laboratory is the clinic!

Acknowledgments and disclosures

CATIE was supported by grant N01-MH-90001 from the National Institute of Mental Health. A list of study locations and principal investigators can be found at www.catie.unc.edu/schizophrenia/locations.html.

The author reports no competing interests.

References

1. Lieberman JA, Stroup TS, McEvoy JP, et al: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. New England Journal of Medicine 353:1209–1223, 2005
2. Moller H-J: Are the new antipsychotics no better than the classical neuroleptics? The problematic answer from the CATIE study. European Archives of Psychiatry and Clinical Neuroscience 225:371–372, 2005
3. Haddad PM, Dursun S: Selecting antipsychotics in schizophrenia : lessons from CATIE. Journal of Psychopharmacology 20:332–333, 2006
4. Bick P, Knoesen N, Castle D: Clinical implications of the CATIE schizophrenia trials: day-to-day management lessons for Australian psychiatrists. Australasian Psychiatry 15:465–469, 2007
5. Owens DGC: How CATIE brought us back to Kansas: a critical re-evaluation of the concept of atypical antipsychotics and their place in the treatment of schizophrenia. Advances in Psychiatric Treatment 14:17–28, 2008
6. Reynolds GP: Receptor mechanisms in the treatment of schizophrenia. Journal of Psychopharmacology 18:340–345, 2004
7. Miyamoto S, Duncan GE, Marx CE, et al: Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Molecular Psychiatry 10:79–104, 2005
8. Owens DGC: A Guide to the Extrapyramidal Side-Effects of Antipsychotic Drugs. Cambridge, United Kingdom, Cambridge University Press, 1999
9. Kinon BJ, Lieberman JA: Mechanisms of action of atypical antipsychotic drugs: a critical analysis. Psychopharmacology 124: 2–34, 1996
10. Kupfer D, Sartorius N: The usefulness and use of second-generation antipsychotic medications. Current Opinion in Psychiatry 15(suppl 1), S1–S30, 2002
11. Rosenheck R, Perlick D, Bingham S, et al: Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophre-

nia: a randomized controlled trial. JAMA 290:2693–2702, 2003

12. Jones PB, Barnes T, Davies L, et al: Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia. Archives of General Psychiatry 63:1079–1087, 2006

13. Rosenheck RA: Effectiveness versus efficacy of second-generation antipsychotic drugs: haloperidol without anticholinergics as a comparator. Psychiatric Services 56:85–92, 2005

14. Baldessarini RJ, Cohen BM, Teicher MH: Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychosis. Archives of General Psychiatry 45:79–91, 1988

15. Baldessarini RJ, Katz B, Cotton P: Dissimilar dosing with high-potency and low-potency neuroleptics. American Journal of Psychiatry 141:748–752, 1984

16. Kane J, Honigfeld G, Singer J, et al: Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Archives of General Psychiatry 45:789–796, 1988

17. Friedman J, Lannon M, Cornelia C, et al: Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. New England Journal of Medicine 340:757–763, 1999

18. Pollak P, Destee A, Tison F, et al: Clozapine in drug-induced psychosis in Parkinson's disease. Lancet 353:2041–2042, 1999

19. Erhart SM, Marder SR, Carpenter WT: Treatment of schizophrenia negative symptoms: future prospects. Schizophrenia Bulletin 32:234–237, 2006

20. Crow TJ: Molecular pathology of schizophrenia: more than one disease process? British Medical Journal 280:66–68, 1980

21. Goldberg SC: Negative and deficit symptoms in schizophrenia do respond to neuroleptics. Schizophrenia Bulletin 11:453–456, 1985

22. Carpenter WT, Heinrichs DW, Alphs LD: Treatment of negative symptoms. Schizophrenia Bulletin 11:440–452, 1985

23. Ramaekers JG, Louwerens JW, Muntjewerff ND, et al: Psychomotor, cognitive, extrapyramidal, and affective functions of healthy volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. Journal of Clinical Psychopharmacology 19:209–221, 1999

24. Artaloytia F, Arango C, Lahti A, et al: Negative signs and symptoms secondary to antipsychotics: a double-blind, randomized trial of a single dose of placebo, haloperidol, and risperidone in healthy volunteers. American Journal of Psychiatry 163:488–493, 2006

25. Baldessarini RJ, Cohen BM, Teicher MH: Pharmacological treatment, in Schizophrenia: Treatment of Acute Psychotic Episodes. Edited by Levy S, Ninan P. Washington, DC, American Psychiatric Press, 1990