Practical Treatment Information for Schizophrenia

Schizophrenia, with its pervasive life impairments and the woeful lack of knowledge regarding its molecular pathophysiology, is a distressing mental illness. Its treatments have been empiric and serendipitously discovered, not rationally understood. Moreover, the treatments are partial, in that psychosis is the treatment-responsive symptom domain, whereas cognition and negative symptoms respond minimally. Successful treatments for schizophrenia, inadequate as they are, have been rather recent. Delay et al. first reported the efficacy of chlorpromazine in 1952 (1), and Carlsson and Lindquist identified the mechanism of that action only in 1963 (2). It is this group of dopamine receptor antagonists—direct and indirect, complex and simple, first and second generation—that we have today as our main treatment tools. While we are quick to point out the inadequacies of these medications, it is certainly true that they are far better than pre-1950 approaches (3).

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We are at a point where we can ask which, among the multiple antipsychotic treatments, are best for effectiveness, efficacy, and tolerability. The Clinical Antipsychotic Trials for Interventions Effectiveness (CATIE) study, sponsored by NIMH, was carried out to answer these questions. The CATIE investigation is a multicenter, multiphase, multidrug study of most of the actively marketed antipsychotics. A total of 1,493 patients entered phase 1 of the CATIE study, the results of which suggested a superiority of olanzapine in length of time to drug discontinuation (4). The hope that other new antipsychotics with fewer metabolic side effects might offer a similar effect was not fulfilled. Some have pointed out that older drugs like perphenazine, with their lower costs, may now once again become rational first-line therapies. The memory of patients with tardive dyskinesia still haunts many clinicians, however. The debate over less expensive first-generation drugs obscures the sobering results of phase 1.

That first report thus also showed once again the stark reality of antipsychotic drugs—their therapeutic limitations and their problematic side effects, especially the metabolic effects. In this issue of the *Journal*, the CATIE story is continued. Stroup et al. report on the CATIE phase 2 "tolerability" study, which compared three second-generation antipsychotics (olanzapine, quetiapine, and risperidone) with ziprasidone (new enough to have missed phase 1) in individuals who had stopped their phase 1 medications for tolerability reasons. In addition, McEvoy et al. report on the CATIE phase 2 "efficacy" comparison of clozapine with second-generation antipsychotics in individuals who had stopped their phase 1 medications for poor efficacy. The CATIE studies are a naturalistic design, purportedly closer to what is done in the "real world" of clinical practice than the industry registration trials. They should more directly inform clinical drug use.

The Stroup study began with 43% of the original cohort and sustained a 74% dropout rate between its study start and end (6 months). Although the dropout rates are substantial, they can be understood in light of a challenging methodology, which allowed patients to continue only as long as they and their doctors thought that they could be successfully treated with the drug selected for them. Both olanzapine and risperidone showed superiority in length of time to drug discontinuation, with quetiapine and ziprasidone lagging

behind. The relative side effect profiles reflect those seen in the phase 1 study, showing olanzapine with prominent weight gain and metabolic changes (increased cholesterol and triglycerides), risperidone with hyperprolactinemia, and no differences across drugs in ECG (including QT interval) measures. Because many clinicians consider the relative dose levels unbalanced, the effectiveness comparisons are difficult to fully benchmark. But, the side effect outcomes are staggering in their magnitude and extent and demonstrate the significant medication burden for persons with schizophrenia.

The McEvoy study began with only 9% of the original cohort (selected from those whose treatment failed efficacy in phase 1); 69% dropped out of the phase 2 between study start and end. The treatment cohort resembles a "treatment nonresponder" group, in that they were predominantly male, older, and had more previous hospitalizations and higher pretreatment psychopathology scores. In contrast to all previous CATIE reports, this "effectiveness" study shows a clear difference in outcome across study groups. Clozapine showed nearly a three-fold increase in time until drug discontinuation compared with the three new antipsychotics olanzapine, risperidone, and quetiapine (10.5 months for clozapine, compared with an average of 2.9 months for the others). Efficacy outcomes are consistent with the time-to-discontinuation measure. The data help answer the critical clinical question, "What to do if a new antipsychotic fails?" The evidence, clearer than many clinicians might have believed, is that clozapine is the only rational alternative. This answer is only tempered by the significantly greater side effect burden with clozapine, again demonstrated: weight gain, increased metabolic measures, sialorrhea, sedation, and the agranulocytosis that we all know to add in (even though adequate surveillance methodology is now in place). But this is a side effect risk profile that is positively balanced by clozapine's increased efficacy and effectiveness. The suggestion by McEvoy and colleagues that we should "develop models of service delivery that would encourage its [clozapine's] greater use" is an idea that is certainly timely. This study strongly confirms what we have seen before, that clozapine is our most effective drug for schizophrenic psychosis.

Several aspects of these two studies may create controversy and challenge us to think creatively about solutions. The possibility of a dose disparity across the administered study drugs, often cited (even in these two articles themselves) as possibly accounting for outcome differences, highlights the crudeness of our dosing measures. To develop equivalent dose ranges across drugs, one needs an objective measure of drug action (other than merely clinical effect); such a goal is currently feasible using human molecular imaging techniques and should be undertaken. Because we know some sites of the molecular site of action (i.e., the dopamine and serotonin receptors), objective dose-equivalence estimates could be derived with additional research. Remington et al.'s report in the March issue of the *Journal*, which used PET imaging to establish a dose range for long-acting risperidone, is an example of such research (5). Also, to aid translation to practice, the CATIE study utilized a new operational definition of effectiveness: treatment discontinuation for any reason. Sky-high drug discontinuation rates were seen, suggesting rampant drug dissatisfaction and inefficacy. However, in the context of this multiphase study, such a high switching rate may reflect the real behavior of conscientious clinicians working with inadequate medications in a setting where drug-switching options are invited. Treatment discontinuation for any reason might be more a measure of physician hopefulness for a next medication than an estimate of failure of the current treatment.

There has not been a previous set of treatment studies that has so clearly shown the tradeoffs for persons who need antipsychotic medication. There is no clear "winner" among the second generation of antipsychotics, weighing effectiveness and efficacy against side effects, nor a clear "loser." It is only clozapine that is superior, although its side effects are clearly challenging. These data make it abundantly clear that the risks and benefits of any single medication need to be weighed individually with each patient, and that side effect risk needs to be weighed repeatedly during treatment. Side ef-

fects need to be continuously monitored and medication adjusted to maintain optimal medical and psychiatric health in the individual person. The CATIE results are packed full of timely, pertinent, interesting, and provocative data pointing up issues about how we should treat, monitor, and advise our patients with schizophrenia in order to help them maximize their health and recovery.

The metabolic and other somatic effects of olanzapine and clozapine also have implications for psychiatric practice. As long as psychotropic medications were considered relatively free of side effects, psychiatrists could practice in settings appropriate to other mental health counselors. However, medication treatments with high side effect burden demand clinical settings that are capable of detecting and managing serious side effects. This knowledge means that the clinician's office needs to be equipped to efficiently monitor antipsychotic drug side effects. Blood pressure cuffs, scales, body tape measures, a process for plasma chemistry monitoring and electrocardiograms, and qualified consultants for medical questions become important components of practice. Dynamic information of drug side effects needs to take a prominent place in a patient's psychiatric chart. Medical consequences of psychiatric drugs are real, preventable, and require focused monitoring. Clinicians will need to have systems for the effective monitoring of drug side effects to maintain and promote physical health among patients as well as psychiatric health.

That these studies were NIMH-funded increases our confidence that they are as free from marketing or other bias or "spin" as possible. However, we do notice that the results of the CATIE studies, although broader and denser than our previous knowledge, are confirmatory of the efficacy and side effect data that we already know—data derived from pharmaceutical studies. This observation should increase our confidence in the results of drug registration studies, limited as they are to the comparative efficacy of one (possibly two) compounds.

Of course, these studies point up the great medical need of schizophrenia. Only knowledge of the molecular basis of this psychotic illness will facilitate rational treatment development. Much remains to be learned. We will have to respond actively to the critical need for new schizophrenia treatments and a real understanding of disease mechanisms with creative research, bold leaps of creativity, and astute clinical observation. The time is right for innovative collaborations between clinicians, basic and translational neuroscientists, and industry to identify research strategies and successful molecular understanding, thereby promoting rational treatments. Moreover, the field must create and sustain teams of people to test innovative treatments, represented most recently by the CATIE consortium.

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