CATIE Phase 2: Clozapine Most Effective, Followed by Risperidone, Olanzapine

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By Richard A. Sherer [1]

There is hope for patients with schizophrenia who do not respond to first-generation antipsychotic drugs: phase 2 results of the CATIE study show that second-generation antipsychotic drugs may be effective.

Phase 2 results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study have been released and appear to demonstrate hopeful signs for patients who do not respond to first-generation drugs for treatment of schizophrenia. At the same time, the results underscore the limitations of most antipsychotic medications for long-term treatment of chronically ill patients.

In phase 1 of CATIE, 1493 patients received either a first- or second-generation antipsychotic drug. More than 70% of the patients discontinued treatment before the end of the 18-month study. In phase 2, 444 patients who had discontinued treatment were randomly reassigned to a second-generation drug: olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), or ziprasidone (Geodon). Another 99 patients who had discontinued treatment agreed to take clozapine (Clozaril), which is known to be more effective than other second-generation medications but carries a greater risk of side effects. Of those patients, 49 received open-label treatment with clozapine and 50 were assigned blindly to olanzapine, quetiapine, or risperidone.

In the group that did not receive clozapine, patients treated with risperidone and olanzapine continued taking their medications longer than those who were treated with quetiapine or ziprasidone. In the group that agreed to try clozapine, patients actually receiving clozapine continued longer than patients taking olanzapine, quetiapine, or risperidone. Forty-four percent of the clozapine patients continued to take the medication for the duration of the 18-month study, as did 29% of the patients receiving olanzapine.

In addition, the authors noted, "at 3-month assessments, Positive and Negative Syndrome Scale total scores had decreased more in patients treated with clozapine than in patients treated with quetiapine or risperidone but not olanzapine."

While the results of phase 1 suggested a superiority of olanzapine in length of time to drug discontinuation, "the hope that other new antipsychotics with fewer metabolic side effects might offer a similar effect was not fulfilled," according to Carol A. Tamminga, MD, who wrote an editorial that accompanied 2 articles reporting phase 2 results in the April 2006 issue of American Journal of Psychiatry.

"The studies continue to provide some data points," said Kenneth Duckworth, MD, medical director for the National Alliance on Mental Illness. "I don't think they give us very many definitive answers. They told us that a group of individuals who were sick for 15 years didn't improve on different compounds. It is interesting to generalize, but these are severely chronically unresponsive patients. Randomly assigning them to different medications doesn't produce any great returns. They were already known to be treatment-unresponsive."

One of the major benefits of the CATIE study may be its independence. The investigation was sponsored by the National Institute of Mental Health (NIMH) and involved 57 treatment sites. The importance of such wide-ranging testing was highlighted earlier this year in a report of another study that appeared in the same journal.

In an article entitled "Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics," Stephan Heres, MD, and coauthors wrote:

"Of the 42 reports identified by the authors, 33 were sponsored by a pharmaceutical company. In 90% of the studies, the reported overall outcome was in favor of the sponsor's drug. This pattern resulted in contradictory conclusions across studies when the findings of studies of the same drugs but with different sponsors were compared. Potential sources of bias occurred in the areas of doses..."
and dose escalation, study entry criteria and study populations, statistics and methods, and reporting of results and wording of findings."
Noting that "the [federal] budget is not being very kind to NIMH," Duckworth said that "the NIMH budget is being cut at a time when a major study has shown there's a chronically ill group that needs treatment. We have a real disconnect there. Schizophrenia is a big cause of disability days for young people. We need to develop third-generation antipsychotics. The CATIE study gives us a reality check. But we don't see progress on research commensurate with the knowledge that it brings."
T. Scott Stroup, MD, MPH, who headed one part of the phase 2 study, echoed Duckworth's call for development of more effective drugs. "It is pretty clear that antipsychotic medicines have substantial limitations," he said in an interview with Psychiatric Times. "They do reduce symptoms, but they have substantial side effects. There are substantial variations between how people might respond, and because the medications have different profiles, the challenge is to find a medicine that works really well for an individual. Treatments do need to be individualized based on responses and side effects."
Joseph P. McEvoy, MD, who headed the comparison study involving clozapine, was not surprised by the results. "We know that clozapine had better efficacy from other studies," he told Psychiatric Times. "If you look at the long-term inpatient units at state psychiatric hospitals, you see that the census took a huge plunge in the early '90s, when clozapine was introduced. In addition, you had lower rates of staff injuries and patient fights. Clozapine has a great capacity to decrease violence, aggression, and suicidal behavior. We have shown clozapine substantially decreases smoking. We found that it not only decreased smoking, but a few people spontaneously quit smoking altogether. Alan Green at Dartmouth has shown similar effects on comorbid substance abuse. But we have no clue as to the mechanism of action."
On the other side of the coin, clozapine carries the risk of severe side effects, ranging from weight gain to agranulocytosis and cardiovascular risk, making it less of a drug of choice for many patients. "If it didn't have the side effects, it would have probably ninety-some percent of the market," McEvoy said. "Its efficacy is better than the others.'"
"Some people who take clozapine are able through diet and exercise to attenuate the cardiovascular risk substantially," he added. "It really is unfortunate that our systems of care do not uniformly offer structured exercise programs for mentally ill patients. People should be out walking every day instead of sitting in a group discussing whatever they discuss."
In the other phase 2 group, patients taking risperidone and olanzapine showed considerably longer time to discontinuation than those taking quetiapine or ziprasidone. "I think time to discontinuation is a nonspecific outcome measure that affects overall acceptability," said Stroup, who headed the team on this part of the study. "We knew that lots of people switch drugs. In our study, people who stopped using a drug usually switched to another one sooner or later. People were actively looking for optimal treatment. The discontinuation rates, which do look high and are a little higher than we expected, were quite consistent with discontinuation rates in studies of, say, Medicaid databases. They were very comparable."
"These medications are not cures," he added. "The best evidence at this point is that patients with chronic schizophrenia are going to continue to need medication indefinitely. Some people may do fine without the medicine, but we don't have any way of knowing who those people are. In general, if the diagnosis is clear and there have been multiple episodes, the recommendation to stay on the medications is also clear. There is a significant proportion of people who find a drug that works well for them and stay with it for a long period of time. For a lot of people, there is an ongoing search for a medicine that may work better."

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